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HYALINE MEMBRANE DISEASE OF NEWBORN PREMATURE LUNGS

A NEW APPROACH

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SINCE Hoecheim[1] described hyaline membrane disease of newborn premature lungs, many hundreds of cases have been reported and many theories have been advanced as to its etiology. Tran-Dinh-De and Anderson,[2] in their excellent review of the literature, list 693 cases reported from 5401 autopsies up to 1952. Of the thirty-six authors quoted by them, twenty-five favored the aspiration theory of causation; of these, fifteen specified aspiration of amniotic fluid. However, this favorite theory has received only poor and sporadic support in experimental fields. The success of a number of unrelated experimental methods in producing hyaline-like membranes in the lungs of animals and the occurrence of similar membranes in a wide range of natural diseases serve to cast further grave doubts on the aspiration hypotheses.

In recent years the membrane itself has been the object of intensive histochemical research, but this also has been rather disappointing. Blystad and associates[3] established the presence of a polysaccharide aldehyde. Wagner[4] recently excluded glycogen, mucopolysaccharides, glycolipids, and phospholipids as possible causes of the positive periodic-acid-Schiff reaction, leaving mucoproteins and glycoproteins to be considered as the responsible agents. Wagner further confirmed the presence of protein in the membranes by the application of Millon's reagent. Analysis of one full-term amniotic fluid in Wagner's laboratory by Dr. I. Bersohn showed that this fluid contained a concentration of mucoprotein thirteen times that of normal human serum. From these findings Wagner concluded that hyaline membranes are formed from endogenous mucus derived from the nasopharynx, buccal cavity, and bronchial tree of the infant.

It is then abundantly clear that there is no agreement or even sound basis for agreement as to the nature and source of the membranes. Here we wish to report our findings and conclusions based on a new approach to this disease.

MATERIALS AND METHODS

1. Frozen sections of formol-saline-fixed material were cut at 15 μ into formol-saline. These were subjected to the Lepehne-Pickworth technique[5]

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as follows: After washing in distilled water for thirty minutes they were placed in the benzidine-nitroprusside mixture in small beakers which were then set in the wax oven at 58° C. for fifteen to thirty minutes, when an equal volume of "double-strength" peroxide (2 ml. of 10 vol. in 70 ml. distilled water) was added and the jars replaced in the oven. At varying intervals from two to fifteen minutes individual sections were removed, placed in distilled water, floated onto slides, dehydrated with graded alcohols and xylene, and mounted in clarite.

2. Similar treatment was given to sections which had been in 5 per cent sodium cyanide solution for five and thirty minutes and eighteen and twenty-four hours.

3. Sections were placed in distilled water in Kolmer-type tubes, which were then immersed in boiling water for six minutes. These sections were then stained by the Lepehne-Pickworth technique.

4. Frozen sections were placed in 1 per cent alcoholic alpha-naphthol for five minutes and then for five minutes in 1 per cent aqueous dimethyl-paraphenylenediamine, then floated onto slides and mounted in glycerol, as the indophenol blue was rapidly removed by alcohol and xylene. Alternatively, it was found that excellent staining by this "Nadi" technique was obtained by immersing the sections for 1 to 5 minutes in a mixture of equal parts alpha-naphthol and dimethyl-paraphenlyene-diamine solutions, to which mixture a few drops of 10 vol. hydrogen peroxide had been added.

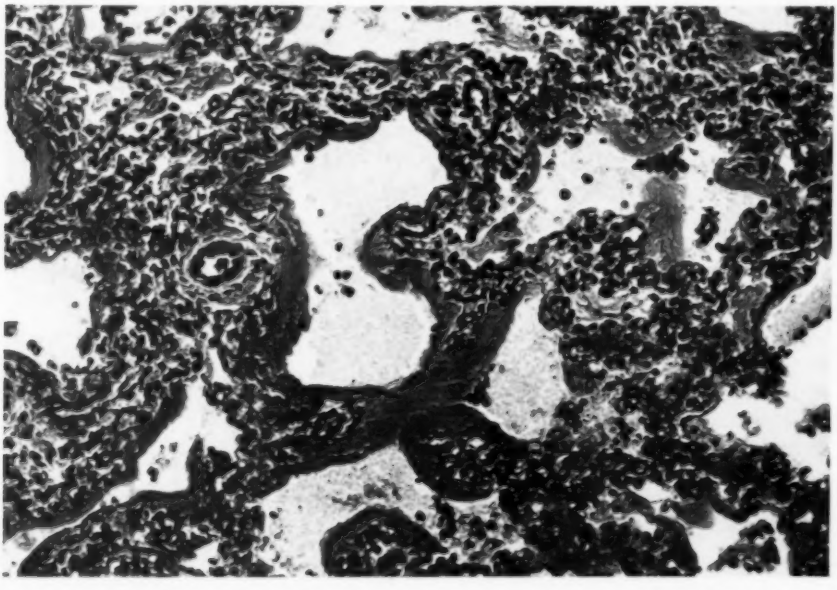

Fig. 1.—Paraffin section of lung of A3/55 showing severe degree of hyaline membrane disease. (H&E; ×300; reduced ¼.)

5. Procedure 4 was carried out on sections which had been exposed to sodium cyanide and boiling as outlined in Nos. 2 and 3.

6. Sections of unfixed material from A3/55, which had been deep-frozen for fourteen days, were cut on the freezing microtome at 20 μ into normal saline. They were then floated onto slides

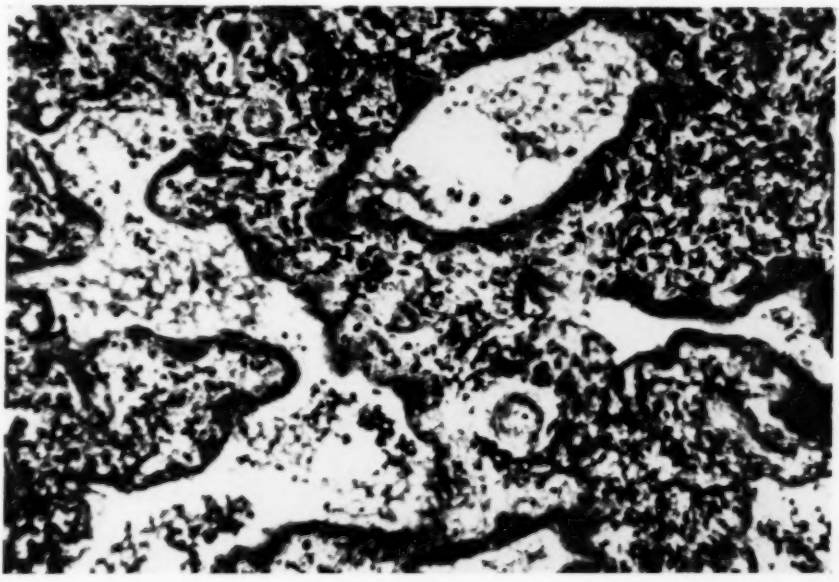

Fig. 2.—Frozen section of lung of A3/55 cut and stained by Lepehne-Pickworth technique after seven days of formol-saline fixation. Note intense staining of hyaline membrane and of red blood cells. (×300; reduced ¼.)

Fig. 3.—Frozen section of A3/55 cut and stained as for Fig. 2. Note red blood cells in hyaline membrane. (×300; reduced ¼.)

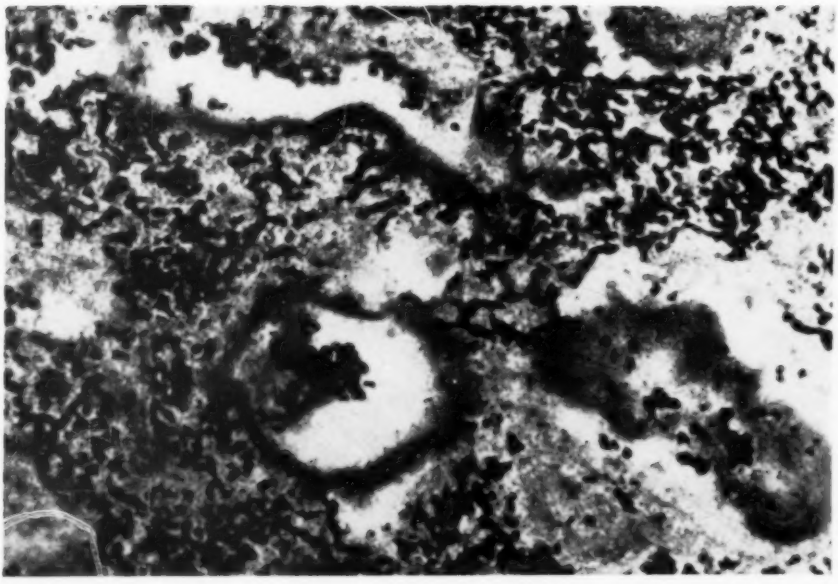

Fig. 4.—Frozen section of lung of A3/55 cut and stained after two months of formol-saline fixation. Note fuzziness and reduced staining intensity of hyaline membrane, while staining of red blood cells is unaffected. (L-P stain; ×300; reduced ¼.)

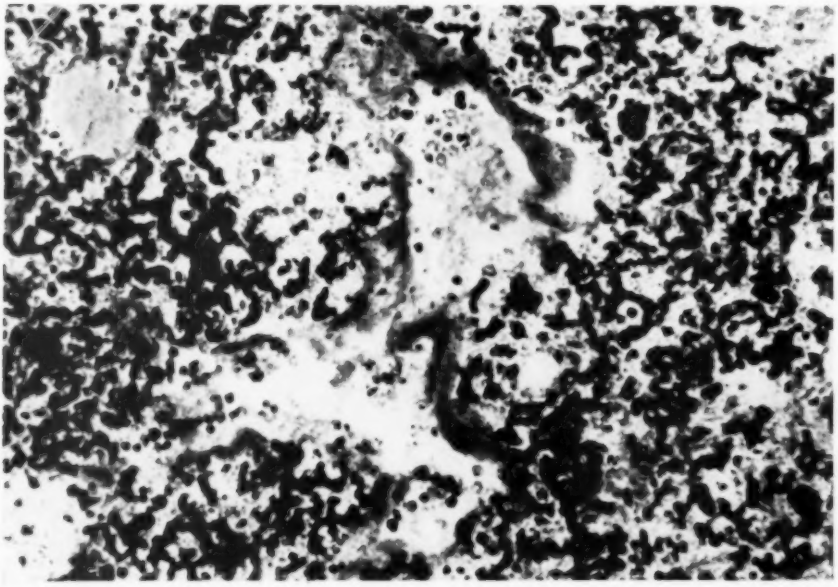

Fig. 5.—Frozen section of lung of A150/54 cut and stained after 5 months of formol-saline fixation. Note reduced intensity of staining of hyaline membrane, which was as severe as in Case A3/55. (L-P stain; ×300; reduced ¼.)

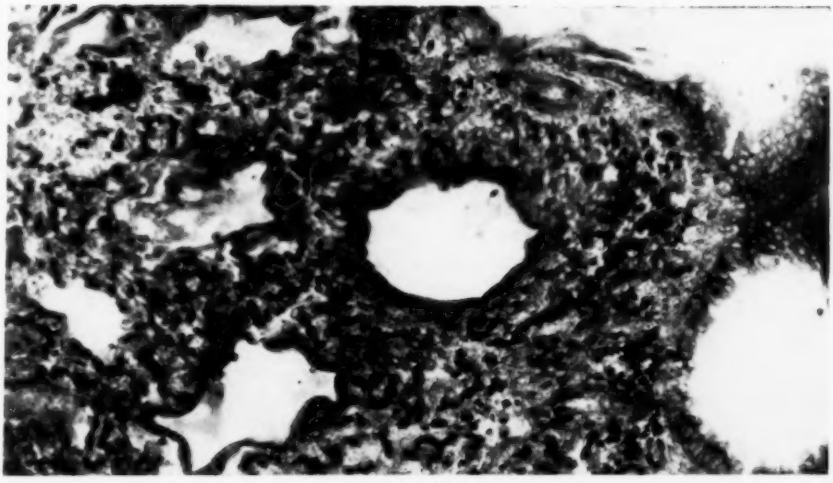

Fig. 6.—Frozen section of lung of A3/55. The hyaline membrane stains sharply and intensely. Fine granules of cytochrome system are present throughout the lung and are more abundant in the epithelium of the respiratory bronchiole. (Nadi stain; ×300; reduced ¼.)

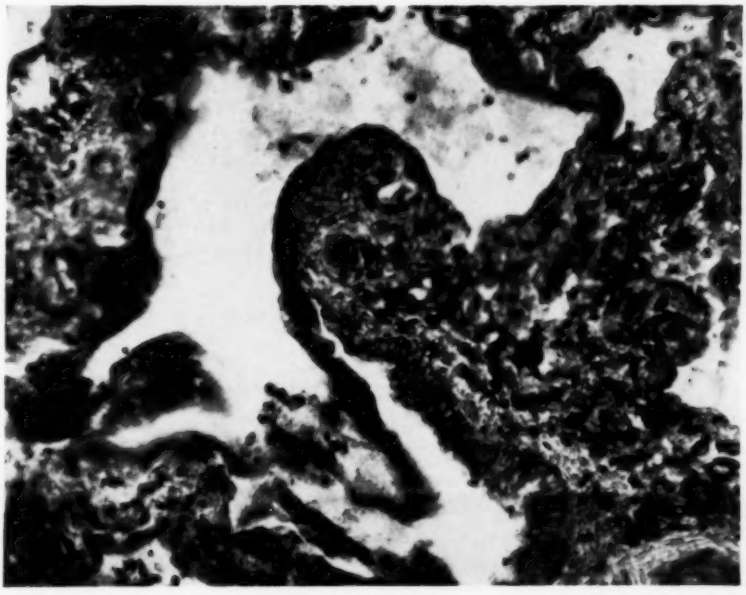

Fig. 7.—Frozen section of lung of A3/55 agitated for two minutes in petroleum ether prior to staining. There is no loss of staining intensity. Note also the relative concentration of cytochrome system granules in the epithelium of the respiratory bronchioles and wisps of secretion coming from these cells. (Nadi stain; ×300; reduced ¼.)

coated with 1:8 dilution of clear human serum and allowed to dry at room temperature. After this they were subjected to the Lepehne-Pickworth and "Nadi" techniques by pouring small amounts of the mixtures on the slides at 58° C. and room temperatures, respectively. These staining procedures were also carried out after treatment with 5 per cent sodium cyanide, 5 per cent sodium azide, and steaming—each for six minutes.

In all, lungs from fifteen cases were investigated. These included four cases of typical hyaline membrane disease of premature infants (Nos. A149,-150 and 201/54, and A3/55). The eleven controls included three cases of uncomplicated prematurity (A130 A and B: twins weighing 12 ounces and 1 pound 13 ounces; and A174/54 weighing 2¼ pounds); a case of acute bronchiolitis in a 2-month-old infant (A172/54); a stillborn infant delivered by cesarean section from a mother dying of 90 per cent skin burns (A170/54); a case of acute bronchopneumonia in a 69-year-old woman suffering from severe burns (A161/54); a case of subdural hematoma in a 57-year-old man (A177/54); a case of acute bulbospinal poliomyelitis in a 4½-year-old girl (A182/54); a case of fibrocystic disease of the pancreas in a 6-week-old boy (A186/54); a case of intra-partum asphyxial stillbirth in a 4½ pound twin (A193/54: cord prolapsed); and a case of bronchopneumonia and cerebral birth injury in a 3-day-old, 7 pound male infant (A8/55).

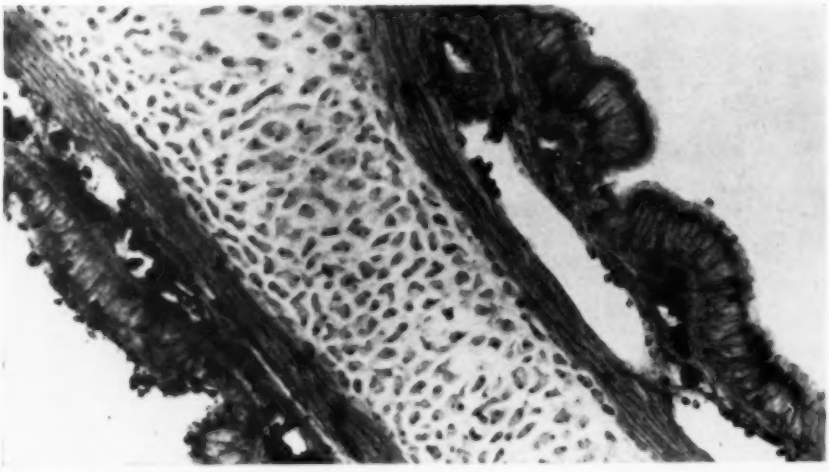

Fig. 8.—Frozen section of finer bronchiole of A3/55. Note the concentration of the Nadi-positive material in the epithelial cells, also the staining of smooth muscle and the discrete location of the cytochrome system in the cartilage cells. The dark clumps are red blood cells. (Nadi stain; ×300; reduced ¼.)

RESULTS

Hyaline Membranes.—The hyaline membranes were stained a uniform deep royal blue by the Lepehne-Pickworth (L-P) technique, which showed the red blood cells as an intense blue-black. This difference enabled one to see the occasional erythrocytes incorporated in the membrane. The lung stroma and alveolar walls showed a diffused background of fine royal blue

granules. In the columnar and cuboidal cells of the respiratory bronchioles and alveolar ducts royal blue granules were significantly more abundant than in the alveolar walls and general lung parenchyma. Indeed, in many respiratory bronchioles the intensity of these granules was such that the epithelium stained a deep uniform blue. Further, in many respiratory and terminal bronchioles it was seen that the blue color became progressively more intense as one approached the luminal or free margins of the epithelial cells. In the majority of fields this transition in depth of color progressed and merged imperceptibly with the rich color of the hyaline membranes which lay directly on the epithelium. A few bronchioles were almost negative in so far as the blue granules were concerned. In almost all cases these bronchioles appeared to be situated in atelectatic lung. In the case of lungs which had been more than three months in Formalin, it was noted that the blue staining of the hyaline membranes was less intense than in more recently fixed tissue. Dr. William Donohue of The Hospital For Sick Children in Toronto has questioned whether this was due to a less intense disease process in the older (long-fixed) cases. To answer this we have cut and stained further sections of A3/55 after two months of fixation. These have shown an undoubted diminution in staining avidity of the membrane after two months of fixation.

Fig. 9.—Frozen section of A150/54. At bottom left is hyaline membrane showing fading of reaction after five months of formol-saline fixation. The dark band at the top is the epithelium of a respiratory bronchiole obscured by dense Lepehne-Pickworth-positive granules—so dense as to form a continuous mass. (L-P stain; ×300; reduced ¼.)

"Nadi" Reaction.—The results were entirely similar, but more clear-cut because in the case of the "Nadi" reaction there was no tendency to crystalline deposit which was often troublesome in the L-P method. This clarity of the "Nadi" reaction enabled one to see a continuous film of "Nadi"-positive secretion lying on many of the cells lining the respiratory bronchioles.

In the case of both the L-P and "Nadi" reactions it was found that when the lung sections were placed in the combined reagents, to which hydrogen peroxide had been added, the sections of relatively fresh material stained rapidly with vigorous evolution of gas bubbles. However, in material which had been in formal-saline for more than one month, though staining took place, no evolution of gas was noted.

Cyanide, Azide, and Boiling.—Treatment of the sections (prior to staining) by each of these methods reduced the intensity of staining to a degree exactly comparable to the reduction seen in tissues which had been fixed for long periods in formol-saline. This reduced staining intensity was seen in the hyaline membrane and respiratory bronchiolar epithelium, but did not affect the erythrocytes.

Fresh (Frozen, Unfixed) Tissues.—With both L-P and "Nadi" reactions, staining was entirely similar to that obtained with freshly fixed tissues. Treatment with cyanide, azide, or boiling reduced the staining intensity.

Controls.—In all cases the epithelium of respiratory bronchioles showed L-P- and "Nadi"-positive fine granules, but these were much less numerous than in the cases of hyaline membrane disease. Further, it appeared that the intensity of staining of the epithelium of respiratory bronchioles and alveolar ducts was inversely proportional to the age of the infant, and was most marked in premature babies. It was noted also that this specific staining of respiratory bronchioles was greatly reduced or even almost absent in unrespired or atelectatic areas of lung. The pulmonary edema present in the case of subdural hematoma showed numerous fine L-P-positive granules. In the lungs of the premature infants which had lived for some time, the L-P technique showed the richness of the respiratory bronchiolar epithelium in royal blue granules, but it also gave a beautiful demonstration of the vascular immaturity of these lungs.

DISCUSSION

The much-favored hypothesis of amniotic fluid aspiration does not bear critical analysis. For such a mechanism to be operative one would have to postulate aspiration of large amounts of fluid in view of its low solid content. Again, if the membranes were so formed, we might expect to find some of this material in the larger bronchioles, but such has never been our experience. Even if all the spaces of the lungs were filled with amniotic fluid during birth, enough solids would not be present to leave such substantial membranes as we see in the natural disease. Alternatively, if one is to postulate that amniotic fluid has been "respired" by the fetus and that this fluid has been concentrated in the alveoli by dialysis, then one has to explain why the disease does not develop within one hour of birth. Again, all of us must have seen many cases without hyaline membranes in which there are many more amniotic squames than

one ever finds in lungs affected by hyaline membranes disease, in which, in fact, amniotic squames are rarely found. Aspiration of amniotic fluid has been advanced as an explanation of the high incidence of hyaline membrane disease in babies born by cesarean section. To explain this on the amniotic fluid basis requires hypothetical gymnastics beyond the grasp of logic, but it may be explicable on the basis of work[6] showing increased incidence of hyaline membrane disease in animals given injections of hormones and high oxygen concentrations. The same may apply in the case of premature babies born of diabetic mothers. Finally, the amniotic fluid aspiration hypothesis must surely retreat in the face of experiments in which hyaline-like membranes are produced without the addition of any foreign substance. Farber,[7] and, later, Miller and coworkers[8] have succeeded in producing hyaline-like membranes in animals (rabbits) by bilateral vagotomy. Pichotka,[9] Clamann and associates,[10] Liebgott,[11] and Burns and Shields[6] have produced similar membranes in animals by exposure to high oxygen tensions; while Becker-Freyseng and Pichotka[12] and Meesen[13] have done the same with carbon dioxide. We have been unable to produce hyaline membranes in artificially respired lungs of suitable stillborn premature babies, into the trachea and bronchi of which both small and large amounts of amniotic fluid and serum, separately and combined, have been injected.

The histochemical evaluation of hyaline membranes has not been rewarding, though batteries of stains have been enthusiastically applied. Many have reported that the mucus stains have been negative.[3, 14, 15] We have used Southgate's mucicarmine stain on several cases of hyaline membrane disease and, while we would not regard the result as positive, we would not report it as an unqualified negative. Indeed, with this stain we have noted in many cases that the hyaline membrane took on the palest of pink colors, but, more significantly, we have noted that the cells lining the respiratory bronchioles are mucus-negative and that only sparse mucus-secreting glands are present in these areas, and these mucous glands are subepithelial in position. For these reasons we have come to base no real weight on the result of mucus stains in this disease.

Our finding that the staining of hyaline membrane by both L-P and "Nadi" techniques is identical with that of the granules in the epithelium of the respiratory bronchioles and alveolar ducts with which the membrane is in contact is strong evidence that it is a secretion of this epithelium. The reduction in intensity of staining by our techniques after prolonged formol-saline fixation, or after treatment with cyanide, azide, or by boiling, points to participation of an enzyme system in the staining reactions, the residual staining affinity being probably due to a metallic complex. However, Hawk, and associates[16] quote the "Nadi" reaction as specific for cytochrome oxidase. It now appears to us that this specificity may be due to the catalytic effect of iron-porphyrin-protein compounds such as the heme of all four members of the cytochrome system or of hemoglobin itself or of catalase, while copper-containing oxidases would likely have a similar effect. The fact that fresh and recently fixed tissues stain in the reagent-mixtures plus peroxide with evolution of gas, where-

as long-fixed tissue stains under these conditions without evolution of gas or with, at most, minimal gas formation, poses a problem in interpretation. In the fresh tissues this could be due to catalase, and by the simple procedure of adding a minute amount (0.1 Gm.) of ground lung to a peroxide solution, we have found that these lungs contain what might be termed explosive amounts of catalase. However, in recently fixed tissues the evolution of gas is probably attributable to metallic catalysts.

Dr. D. Bowden of The Hospital For Sick Children, Toronto, has drawn to our attention the claim that indophenol blue (end product in the "Nadi" reaction) is a lipid stain. However, we have shown that the "Nadi" reaction fails to stain the lipid vacuoles in fatty livers, and we have found that hyaline membranes are stained by this technique after prior two-minute agitation of the sections in xylene or petroleum ether, which procedure also has no effect on subsequent staining by the Lepehne-Pickworth technique. This finding would seem to us, in addition, to exclude a peroxidized-polymerized lipid as the cause of the "Nadi" staining of hyaline membrane—unless the lipid is closely bound to protein groups.

The possibility that the positive L-P and "Nadi" reactions may be due to red blood cell heme liberated by hemolysis has occurred to us. However, this seems to be highly unlikely for several reasons, chief of which are the facts that there is no evidence of hemolysis or of hemolytic pigment in ordinary sections and that the uniformity of staining by both the L-P and "Nadi" reactions is such as is most unlikely to result from dispersal of products of hemolysis, while the selective concentration of the royal blue granules in the epithelial cells of the respiratory bronchioles is further evidence against the hemolysis possibility. Last, where hemolysis was intentionally produced by cutting sections of unfixed lung (A3/55) into distilled water, all the products of hemolysis were washed out and there was no alteration in the staining intensity of the membranes or of the general lung parenchyma. However, it is still possible that the reacting substance in the membrane may be an insoluble hemoglobin precipitate, though we do not consider this likely as we have ample color photomicrographic evidence to show active secretion of the membranes from the epithelial cells of the bronchioles and alveolar ducts. To our knowledge there is no evidence that hemoglobin is secreted by any cells—unless fetal hemoglobin is an exception!

While we are unable to identify the reacting substance in the membrane, we feel that it is clear from our work that the membranes represent a concentration of excessive secretion of the epithelial cells of the respiratory bronchioles and alveolar ducts. The reacting substance, we feel, will likely prove to be a metallic (copper or iron) component of a system which, one would like to think, plays an active part in the transfer of oxygen across the lung-hemoglobin barrier. However, in the present state of our knowledge any such ideas cannot be more than speculative. Our investigations have shown that the reacting substance(s) is present throughout the lung parenchyma and in the smooth muscle of the bronchioles and blood vessels, but they have shown also that it is selectively concentrated in, and almost certainly secreted by, the epithelium of

the finer bronchioles. Our observation that unrespired lungs are relatively poor in this L-P- and "Nadi"-reacting substance may mean that oxygen is required for the activation and/or secretion of the substance(s). In this connection it might be recalled that oxygen is required for the activation of the cytochrome system.[16] Should this be proved it would answer the question, "Why does hyaline membrane disease not develop within approximately one hour of birth." The significance of this latent period and the importance of respiration were impressed upon us by the findings in a case of left-sided complete diaphragmatic hernia in a premature infant which lived a few hours. Early hyaline membrane formation was seen in the unaffected right lung, but was completely absent in the left lung which was rendered entirely atelectatic by the presence of stomach, spleen, and parts of small and large intestine in the thoracic cavity of that side.

The production and secretion of the reacting substance as demonstrated by us, be it a metallic-porphyrin-protein complex or some hitherto unknown system, may be governed by laws of "mass action demand," that is, presupposing that its function is to facilitate gaseous transfer in the lung. Were this so, then it would be reasonable to postulate that the amount of complex secreted would be in proportion to the amount of oxygen exhibited. This would explain many things, including both the experimental production of hyaline membranes by exposing animals to high oxygen concentration and the deleterious effects of high oxygen tensions in the production of both hyaline membrane disease and retrolental fibroplasia. In relation to this speculation it may be mentioned that Dr. D. H. Weintraub of Buffalo has noted virtual abolition of retrolental fibroplasia and a marked reduction in the incidence of of hyaline membrane disease in his hospital since the use of oxygen was severely curtailed.

Our experiments have convinced us that the lungs of premature infants differ from their full-term counterparts both in the excessive secretory evidence in the terminal bronchioles and in their incomplete vascularization of atrial walls. The vagotomy experiments of Farber may be closely parallel to conditions as they exist in the lungs of premature infants in that vagotomy likely acts by allowing excessive secretion, possibly of increased consistency, while inhibiting the cough reflex. It is interesting to speculate that in premature infants there is an incompletely developed control of bronchiolar secretion and a poor cough reflex and, perhaps, also weak or even reversed ciliary action. In the lack of neural control of secretion we feel that there is an analogy also between hyaline membrane disease and the pulmonary edema of cerebral trauma. In the case of premature infants under 1,000 Gm., who rarely develop hyaline membrane disease, we believe that the gross immaturity of alveolar walls and vasculature as shown by our technique are sufficient to preclude recognizable development of hyaline membranes before death would occur.

It is conceded that low humidity increases the incidence and severity of hyaline membrane disease.[18] This would seem to be very logical since it would lead to drying and plastering of the membrane against the cells which secrete it. It is likely that time will show that high humidity and low

oxygen concentration are two essentials in the prophylaxis of this disease, while the use of drugs which specifically inhibit bronchiolar secretion may also be worthy of investigation.

SUMMARY

Pulmonary hyaline membranes of the natural disease of premature newborn babies were studied by the application of the Lepehne-Pickworth and "Nadi" techniques, using frozen sections of fresh and Formalin-fixed material. The membranes were stained an intense blue by these methods. The epithelium of respiratory bronchioles and alveolar ducts contained a selective concentration of granules with similar staining reactions to those of the membranes. The reactions were partly inhibited by prior treatment with cyanide, azide, or steaming, and by prolonged fixation in formol-saline, and are believed to be due to metallic complexes possibly forming part of an enzyme system. The investigations have led us to conclude that hyaline membranes represent a highly concentrated secretion from the epithelial cells of the terminal bronchioles and alveolar ducts.

We wish to express our thanks to Dr. W. L. Donohue, director of pathology, The Hospital For Sick Children, Toronto, to Dr. D. Bowden of his department for helpful criticism and advice, and to Dr. J. Hamilton, professor of pathology, University of Toronto, for his encouragement.

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ASSOCIATION OF ESCHERICHIA COLI 0127:B8 WITH AN OUTBREAK OF INFANTILE GASTROENTERITIS AND ITS CONCURRENT DISTRIBUTION IN THE PEDIATRIC POPULATION

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THE role that certain serotypes of *Escherichia coli* play as inciters of infantile diarrhea is well known. Since Bray's[1] demonstration in 1943 of *Bacterium coli neapolitanum* (0111:B4) as one of the etiological agents of this disease, reports involving this organism and other coli serotypes in epidemics have come from all over the world.[2-7] Recently still newer coli serotypes have been noted to be associated with infantile diarrhea.[8, 9] From an epidemic of infantile gastroenteritis in Cincinnati, Ohio, Cooper[10] early in 1954 isolated an organism that Dr. William Ewing at the National Escherichia Center typed as *E. coli* 0127:B8. The bacteriology of this serotype has been described in a paper by Ewing and associates.[11] In the past year papers still in press have linked this particular strain to epidemics in Philadelphia, Pennsylvania, Gary, Indiana, and Kamloops, British Columbia.[12-14]

Presented herewith is the report of an infantile gastroenteritis outbreak at the Colorado State Children's Home involving *E. coli* 0127:B8, together with an assessment of the incidence of this organism in the Denver pediatric population.

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MATERIALS AND METHODS

Cultures for both outbreak and survey were obtained by rectal swab from the patients at the Children's Home, nurseries, well-baby clinics, and diarrhea wards of eight Denver hospitals. All swabs were plated immediately on blood and eosin-methylene blue agar for growth. Following incubation, at least three colonies from these media were then selected for biochemical study by streaking for purity to a blood agar plate. Those colonies which gave appropriate IMViC reactions and which failed to ferment the carbohydrate galactinol[15] were submitted to antigenic analysis. For this purpose three lots of polyvalent serum containing nine sera were used. Lot 1 contained types 0111:B4, 055:B5, and 026:B6. Lot 2 contained types 086:B7, 0119:B14, and 0125:B15. Lot 3 contained types 0126:B16, 0127:B8, and 0128:B12. Positive agglutination in any lot was investigated further with the individual component sera. All sera* were made from the whole organism and contained agglutinins for both O and B antigens. The methods for antigenic analysis were essentially those of Enteric Unit, Communicable

*Sera used for this study were graciously supplied by Dr. Wm. Ewing, Communicable Disease Center (CDC), Chamblee, Ga., and by Dr. Joan Taylor, Salmonella Reference Laboratory, Colindale, London, England.

Disease Center, and have been outlined in a pamphlet obtainable from that agency. All positive cultures were confirmed by the CDC Laboratory.

The Children's Home is maintained for the care of the dependent children of Colorado. The nursery where the outbreak occurred is a separate building in which children under 2 years of age are cared for. Of the twenty-nine children in the nursery at the time of the epidemic, fourteen were between the ages of 3 and 24 months. These were all permanent residents of the nursery since they were poor adoption material, i.e., mixed blood, poor mentality, or congenital defects. The remaining fifteen were all under 3 months of age. Normally, this group would have been transients, staying in the home only a short while before being placed in adoption homes.

Although the infants were separated by age and grouped four or five to a glass-partitioned room, the employees circulated from room to room with little isolation procedure being used. The older children were often fed in the kitchen where the infants' formulas were prepared. At the time of the epidemic, terminal sterilization was not being used and the possibility of spread of any organism through the nursery by means of food, milk, or person-to-person contact was great.

Since the early patients with diarrhea had been discharged from the nursery prior to the onset, some time elapsed before the home was aware of the epidemic. On Nov. 9, 1954, when the problem was recognized, the nursery was closed to all new admissions, and because of the risk of an infant becoming ill in an adoption home, discharges were also stopped. Terminal sterilization was instituted and general technique was improved. Stool cultures were taken from all infants and personnel in the nursery. Negative cultures were obtained from the nipples, sinks, scales, and sterilizer.

On November 16 it was found that the stool cultures of eleven of the twelve infants under 3 months of age were positive for *E. coli* 0127:B8, and at that time five of these infants were not ill. Because of the reports of Wheeler and Wainermann[16] dealing with *E. coli* 0111:B4, all infants in the home were treated with neomycin in Kaopectate 50 to 75 mg. per kilogram for five days. Sensitivity studies later showed this organism to be sensitive to both neomycin and chloramphenicol.

RESULTS

Of the fourteen children from 3 to 24 months of age, none developed diarrhea or had a positive stool culture. These infants did not receive any neomycin therapy.

None of the eight attendants had gastrointestinal disturbances, although two did develop positive stool cultures.

Of the fifteen infants younger than 3 months, twelve (80 per cent) became ill. Among the twelve sick infants there were four deaths (33 per cent). Ten cases were culturally confirmed as *E. coli* 0127:B8. Since the other two died prior to the recognition of the epidemic, they were never cultured.

Fig. 1 illustrates the relationship of illness, positive cultures, and neomycin therapy among the infants.

Four infants became ill after discharge from the nursery—one, three, and six days elapsing between their time of discharge and their onset of illness. The infant who became ill six days after discharge had only been in

the nursery for three days. Because of a vague history, the exact date of onset in the fourth infant was not determined. Two infants became ill loss, irritability and lassitude. Some regurgitated or vomited part of their feeding, while in three cases the vomiting was a main symptom, one being

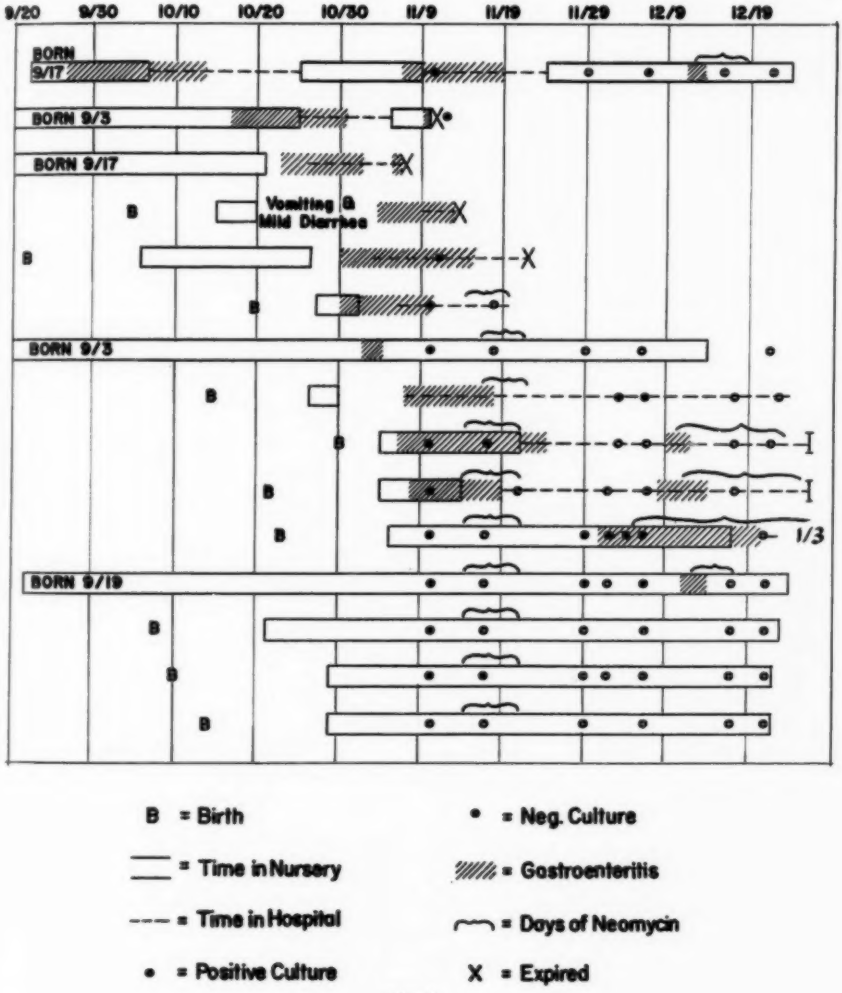

Fig. 1.

within forty-eight hours of their arrival in the nursery.

The onset was manifest in general by loose stools, low-grade fever (99° to 101° F.), failure to gain or weight of such severity and projectile in nature that a pyloric stenosis was diagnosed and the infant operated upon. Severity of the diarrhea varied from a few loose yellow stools to frequent

(every hour) watery, green stools. Weight varied from a failure to gain to a 19 ounce loss in four days. Relapses occurred in five cases which, in contrast to the initial phase, were abrupt and more severe.

Two infants died in the initial phase and two died in a relapse. The autopsy findings all were consistent with a subacute gastroenterocolitis, there being congestion and mucosal infiltrates of eosinophils, lymphocytes, and plasma cells in all sections. In addition, all had a complicating factor such as: (1) hypoplastic adrenals (combined weight 1.8 grams), ascites, emaciation, dehydration, and agonal aspiration of gastric contents; (2) surgery complicated by a perforation of the duodenum and generalized subacute peritonitis; (3) massive thrombosis of the mesentery, portal, and splenic veins; and (4) excess administration of intravenous fluids.

Ten of the fifteen infants under 3 months of age had already developed diarrhea prior to the time neomycin was given; therefore, it is hard to evaluate the effect neomycin had on the epidemic.

Five infants were healthy before the drug was given. Four of these had positive cultures. After neomycin therapy, two were still positive and subsequently developed diarrhea; two became culturally negative and remained well; the fifth healthy infant remained well and culturally negative throughout the epidemic.

Seven infants did not receive neomycin therapy; of these, two died during the initial episode, two more died during a relapse, and one developed a relapse which responded promptly to neomycin therapy. The remaining two infants were given a course of neomycin during convalescence because of a positive culture. Their cultures were negative after the neomycin therapy.

Of the five infants treated with neomycin, four responded with cessation of symptoms, although two developed relapses. Positive cultures were not obtained during their relapses; however, none died.

Since a survey of the pediatric population of Denver for several other coli serotypes had already been reported by Graber and Dunlop[17] with apparently negative results, it was felt a study of the city should be made for *E. coli* 0127:B8 to determine its concurrent incidence at the time of the epidemic. Because of the age distribution of the cases in the Children's Home, only infants under one year of age were cultured.

Cultures of eighty-six babies in eight hospital nurseries were all negative. Only prematures and term infants over five days of age were included. Forty-two cultures from healthy infants 1 to 6 months were also negative for *E. coli* 0127:B8. However, from one infant 3 months of age an *E. coli* 0126:B16 was recovered.

Three hundred twenty-seven babies with diarrhea not related to the Children's Home outbreak were cultured. Of this group, two isolations of *E. coli* 0127:B8 were made.

One of these infants was treated with neomycin and made a prompt recovery. The second infant died of diarrhea and dehydration on his eighth hospital day.

In addition, among the children with diarrhea there were two isolations of *E. coli* 0111:B4.

DISCUSSION

Emphasis on the role of specific serotypes of *E. coli* as the causative agent of infantile gastroenteritis continues to be predicated on the epidemiologic evidence that cases and contacts yield organisms of the same serotype. Attempts to demonstrate serum agglutinins and hemagglutinins[18] have been successful in only some cases and this procedure has not been widely used because of the evanescent quality of the antibody.

Difficulty in finding human volunteers makes feeding experiments equally impractical. The presence in institutional outbreaks of asymptomatic infants harboring the same organism as actual cases does not invalidate etiological significance. We feel, as does Dr. Joan Taylor,[19] that a particular strain of *E. coli* may or may not have additional properties on which pathogenicity depends. Alternately, the resistance of infants may vary and, perhaps, as has been shown with the Salmonella,[20] it may merely be a matter of numbers.

The case for the etiological role of *E. coli* 0127:B8 in the outbreak described here is as follows:

In each case of gastroenteritis which was cultured, *E. coli* 0127:B8 was recovered in almost pure culture. In two fatal cases, cultures were not secured, but since the course for these cases was similar, the presumption that *E. coli* 0127:B8 would have been recovered seems strong. In two of the three asymptomatic infants *E. coli* 0127:B8 was recovered, and following neomycin administration these infants never became ill. The third infant had negative cultures before and after neomycin therapy. It is possible that neomycin may have been a factor in preventing this infant's infection. In addition, the recovery of but two *E. coli* 0127:B8 isolated from a survey of 455 infants, 327 of whom had diarrhea, ruled against the possibility of *E. coli* 0127:B8 being widespread in the Denver pediatric population. It is interesting that these two survey recoveries were from acutely ill infants, one of whom died.

This epidemic offered an unusual situation to observe the age specificity of this organism. Despite continued exposure, the children over 3 months of age never developed positive cultures or any signs of gastrointestinal disease. This was in contrast to the employees who had a more direct contact with the infected infants. Two of the eight attendants developed positive cultures.

Since we have been able to recover the organism from the nose and throat of infants with diarrhea as well as from the stools, the organism may well have spread by means of the fecal-respiratory route to the attendants during the process of changing diapers. Perhaps masks would have helped prevent the infection of attendants and possibly prevented the spread through the nursery.

The effect of neomycin on the epidemic is difficult to analyze. While the patients seemed to respond to treatment and fewer cases occurred after the drug was given, this may have been the natural course of the outbreak. It was the feeling of the clinicians, however, that the drug had a beneficial effect in aiding the patients' recovery and preventing relapses. Perhaps the two patients who developed diarrhea after their prophy-

lactic course of neomycin should have been retreated until a negative culture had been obtained.

SUMMARY

1. An epidemic of gastroenteritis in an adoption home associated with *Escherichia coli* 0127:B8 has been described. It is postulated that this organism was the etiological agent.

2. Neomycin in Kaopectate may have been effective treatment and prophylaxis in this epidemic.

3. Cultures of 128 well infants and 327 sick infants from Denver during the time of the epidemic yielded only two positive cultures of *E. coli* 0127:B8. Both of these infants had diarrhea.

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CONGENITAL TRACHEO-ESOPHAGEAL FISTULA WITHOUT ESOPHAGEAL ATRESIA

An Endoscopic Diagnostic Technique

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THE presence of congenital tracheo-esophageal fistula without atresia of the esophagus can be strongly suspected on clinical grounds alone, but the proof of its existence is frequently very difficult. The usual radiologic and endoscopic techniques employing radiopaque oils have often been inconclusive. In the past ten years, three infants with this anomaly have been seen at the St. Louis Children's Hospital. The last two infants were diagnosed by the relatively simple endoscopic technique to be described and were corrected by surgical closure of the fistula.

INCIDENCE

The true incidence of any congenital anomaly is difficult to determine. Tracheo-esophageal fistula associated with esophageal atresia is said to occur once in every 500 live births in the Boston area and less than one in every 10,000 live births in Philadelphia.[1] In these instances of tracheo-esophageal fistula, probably 97 to 99 per cent are associated with esophageal atresia. The remaining 1 to 3 per cent of these infants with tracheo-esophageal fistula have a normal esophagus and are of the type described in this paper (Fig. 1). Of approximately 4,000,000 babies born each year in the United States, between 4 and 240 of them will have tracheo-esophageal fistula without esophageal atresia.

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ANATOMY

The embryologic explanation for this anomaly has been well described by Gengenbach and Dobos.[2] "About the time when the embryo reaches a length of 4 mm., two lateral indentations or grooves appear on either side of the entodermal sac, which gradually become deeper and, when they meet in the center, form the septum, dividing the entodermal sac into an anterior tube which belongs to the respiratory system and the posterior tube which belongs to the alimentary system. The completion of the septum takes place first in the caudal end of the pouch and it extends subsequently upward in cranial direction." The septum is completed when the embryo is about 11 mm. in length. Developmental arrest or failure in the completion of this septum will result in a tracheo-esophageal fistula. The fistula is most commonly near the carina, but it may be located several centimeters proximal to the tracheal bifurcation, sometimes even occurring just below the vocal cords. The esophagus is patent and appears to develop normally in other respects.

SYMPTOMS AND SIGNS

The symptoms produced by this anomaly, as exhibited by our cases, are

fairly characteristic: (1) When the newborn infant is first fed sterile water or formula, symptoms of coughing, choking, and cyanosis will result. These same symptoms recur when he is again fed. These infants exhibit no difficulty with swallowing. They take the nipple eagerly, swallow well, and a second or two later exhibit respiratory distress. Esophageal atresia is quickly ruled out by the passage of a catheter down the esophagus into the stomach. (2) On auscultation of the infant's lungs before and immediately

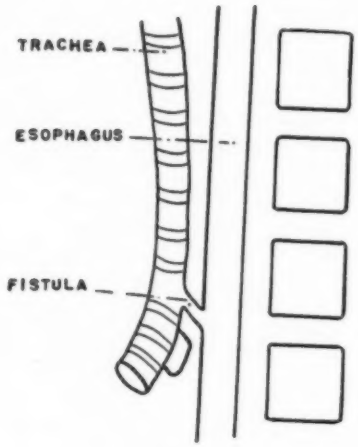

Fig. 1.

after a feeding, the examiner will be struck by the discrepancy between the originally clear lung fields and the subsequent diffuse râles and rhonchi. (3) The infant's symptoms entirely disappear or are vastly improved if he is fed by intermittent gavage or by an indwelling plastic nasogastric tube. Occasional bouts of aspiration may still occur in these gavage-fed infants if feedings are regurgitated from the stomach up into the esophagus and then through the fistula. This is more likely to occur if the infant is in the prone position. (4) Characteristically these infants tolerate solid foods by mouth better than liquids, and as a rule they have less trouble with milk than they do with water. (5) Another typical feature of tracheo-esophageal fistula without associated esophageal atresia is the rapid appearance of marked gastric distention when the infant cries and strains.

ENDOSCOPIC AND RADIOGRAPHIC DIAGNOSIS

The demonstration of a tracheo-esophageal fistula by endoscopic and radiographic techniques is usually difficult. Varying techniques have been advised by different authors, but they stress that repetition of diagnostic procedures is usually necessary. The following methods have been employed: (1) Esophagoscopy. This is of little value. A small fistulous opening is seldom visualized and may be obscured by the esophageal mucosal folds. (2) Tracheoscopy. Since the trachea is a more rigid structure than the esophagus, the lining mucosa is less likely to obscure the opening of the fistula. This method has been successful in a 6½-year-old boy described by Imperatori[3] in 1939. He was able to pass a ureteral catheter through the fistula and successfully closed the fistula through a cervical tracheotomy incision. This was the first successful surgical cure of this condition. Abbott[4] has suggested that the patient be given a swallow of methylene blue prior to tracheoscopy because the fistulous tract may be more easily visualized if it is stained with dye. (3) Esophagogram. An esophagogram, employing Lipiodol, 35 per cent Diodrast or 30 per cent Urokon, has occasionally demonstrated a fistula. Barium

should never be used because of the danger of a resultant barium pneumonitis. In our experience, Lipiodol, even when warmed to body temperature, has been too viscous, and presumably surface tension is great enough to prevent the oil from entering the fistula. This has likewise been the experience of Cardullo and Berens.[5] It is of paramount importance that the patient be in proper position when x-ray films are taken. In the anteroposterior position the trachea and esophagus overlie one another, and the fistulous tract will not be thrown into relief. The right or left anterior oblique position (in relation to the table top) is to be preferred. The contrast medium is best administered through a catheter placed in the upper esophagus. The x-rays must be taken at the proper moment after injection of the contrast medium as determined by fluoroscopic observations. Fistulas have been demonstrated by this technique by Ferguson,[1] and by Leigh and associates.[6] Despite repeated attempts in our Cases 2 and 3, we were unable to demonstrate the presence of a fistula by this technique. (4) Tracheogram. A catheter is inserted into the trachea to a level just below the vocal cords, and with the patient in the right or left posterior oblique position (in relation to the table top) the contrast medium is instilled and films are taken as indicated by fluoroscopic observation. Ferguson[1] demonstrated a fistula in two cases by the tracheogram technique.

METHOD OF ENDOSCOPIC AND RADIOLOGIC EXAMINATION

The most important prerequisite to a successful demonstration of the presence of a tracheo-esophageal fistula is the cooperation and combined efforts of a diagnostic team consisting of pediatrician, endoscopist, anesthesiologist, and radiologist. The following equipment is needed:

1. A standard x-ray tilt table with fluoroscopic and spot-filming device.
2. Endotracheal intubation setup with oxygen and suction machine.
3. Mosher infant esophagoscope with suction tube. A small polyethylene tube that will pass through the endotracheal tube.
4. 20 c.c. Luer-Lok syringe with the proper-sized needle to fit into the polyethylene tube. Alcoholic methylene blue, saline, and 30 per cent Urokon.

PROCEDURE

With the infant in a supine position, induction is started with open drop ether. The endotracheal tube is passed and the patient is carried into a deep plane of anesthesia with gas, oxygen, and ether. The endotracheal tube is withdrawn slightly under fluoroscopic guidance until its end is just distal to the true vocal cords (Fig. 2). Then the infant-sized esophagoscope is inserted so that its tip is just beneath the cricopharyngeus, roughly corresponding with the level of the endotracheal tube. A small polyethylene tube is passed through the endotracheal tube until its end has just cleared the end of the endotracheal tube. With the endoscopist closely watching through the esophagoscope, 1 or 2 ml. of a methylene blue-tinged normal saline solution (20 ml. of normal saline containing two or three drops of alcoholic methylene blue) is rapidly injected through the polyethylene tube. If a fistula is present, the endoscopist will see a sudden gush of blue fluid pour through the fistula into the esophagus distal to the esophagoscope. If, when it is first visualized, the dye

is far distal to the esophagoscope, the esophagoscope is advanced until the dye enters the esophagus through a small indistinctly visualized anterior opening immediately in front of the esophagoscope.

A lateral x-ray of the chest taken at that time with the esophagoscope in place will give the exact level of the fistula, the bifurcation of the trachea providing a point of reference.

In attempting to outline the fistulous tract and get a permanent x-ray record of its presence, 1 or 2 ml. of 30 per cent Urokon tinged with methylene blue can be instilled into the polyethylene tube and films taken in either right or left posterior oblique position. The film exposure is made at the instant the endoscopist sees the material flood over into the esophagus. To date we have not been successful in obtaining films that are diagnostic of a tracheo-esophageal fistula despite the definite endoscopic proof of its presence.

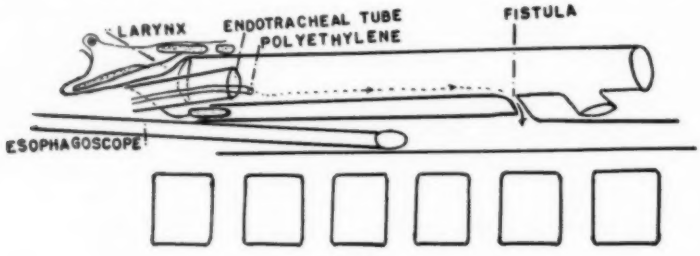

Fig. 2.

Thus having secured proof as to the presence of a tracheo-esophageal fistula and an idea as to its approximate location, the thoracic surgeon can then proceed with surgical closure of the fistula.

CASE REPORTS

Case 1.—V. F., a 1-month-old white female infant, was admitted to the St. Louis Children's Hospital on Sept. 14, 1944. She was a full-term baby, weighing 6 pounds 12 ounces at birth. Labor and delivery were normal. There was apparently some atelectasis present initially, but this gradually cleared. Shortly after birth it was noted that the infant coughed with each feeding, and a few days later coughing also occurred between feedings. At the time of hospital admission she weighed 5 pounds 15 ounces. Physical examination revealed a thin, undernourished infant who did not appear acutely ill. If one listened to the infant's lungs between feeding periods they were clear except for slight diminution of breath sounds over the right lower lung field. During feedings there was a deep rasping cough, and the lungs at that time contained diffuse coarse râles. The abdomen became quite distended at intervals. A barium swallow done under fluoroscopic observation showed no abnormality of the esophagus. Chest x-ray revealed patchy atelectasis of both lungs. On September 20 the infant regurgitated, aspirated, and became quite cyanotic. The baby's color improved promptly, and she was subsequently discharged on Sept. 24, 1944. Diagnosis on discharge was questionable tracheo-esophageal fistula, congenital.

The infant was readmitted to the hospital two days later because of severe continuous cough. Physical examination revealed findings of right lower lobe pneumonia. The abdomen was distended, and there were numerous dilated superficial abdominal veins. Direct laryngoscopy revealed the mu-

cous membrane of the larynx was chronically injected and thickened. Otherwise the larynx and epiglottis were normal in appearance. The patient's clinical course was one of continued coughing spells during feeding. Whenever the baby cried, the abdomen rapidly became distended, and these intermittent periods of extreme abdominal distention caused greatly increased respiratory distress. There were episodes of pneumonia which cleared somewhat on sulfadiazine and later on penicillin therapy. The patient's course was gradually downhill, and she died on Dec. 18, 1944, at the age of 4 months.

Post-mortem examination revealed the presence of a tracheo-esophageal fistula, 3 mm. in diameter. This was situated 2 cm. above the carina and 8 cm. above the cardia of the stomach. There was bronchopneumonia throughout all lobes of the lungs and considerable purulent material in the tracheobronchial tree.

CASE 2.—D. S. K., a 6-week-old white female infant, was admitted to the St. Louis Children's Hospital on May 8, 1952. She was a full-term infant, weighing 6 pounds 11 ounces at birth. Cry and respiration were spontaneous. The day following delivery the infant was said to have developed atelectasis of one lung. She was treated with penicillin and oxytetracycline and fed entirely parenterally for a one-week period. Following resumption of oral feedings the infant would cough, develop a "rattle in her throat," and become slightly cyanotic whenever she took a few swallows of formula. She was given a barium swallow, and because she aspirated some of the barium she was referred to this hospital.

Physical examination showed an active 7 pound 5 ounce infant. There was no cyanosis. There were rhonchi throughout both lungs. The heart was normal as was the rest of the examination. The following day a Lipiodol swallow was performed which showed slight narrowing of the esophagus somewhat above the level of the bifurcation of the trachea. There was prompt appearance of contrast material in the trachea without evidence of it in the pyriform sinus which suggested that the Lipiodol entered the trachea by a fistula rather than having been aspirated. The fistulous tract was at no time demonstrated. On May 12, 1952, a tracheogram was attempted, but each time the catheter touched the vocal cords there was respiratory distress with the cords in spasm. The procedure was, therefore, discontinued. The infant was fed by nasogastric tube and had no coughing spells or respiratory distress. Further diagnostic procedures were delayed because the infant developed mild diarrhea. On June 5, 1952, with the patient in the supine position, under endotracheal anesthesia, a small polyethylene catheter was inserted into the endotracheal tube and Lipiodol instilled and x-rays taken. No definite fistula was seen. An esophagoscope was inserted into the esophagus, and a small dimple was seen on the anterior esophageal wall at about the level of 1½ cm. above the carina. Then methylene blue in saline solution was instilled into the small polyethylene tube inserted into the endotracheal tube. The operator closely observed the esophagus at the moment of injection, and dye was seen to flood over into the esophagus proximal to the level of the bifurcation of the trachea. On June 9, 1952, a right thoracotomy was performed, and a tracheo-esophageal fistula was found at the level of the apex of the chest. This was divided and both ends closed. The postoperative course was smooth. She took feedings by mouth on the second postoperative day without difficulty. She was discharged in good condition on the fifteenth postoperative day. She is now in good health at the age of 3 years.

CASE 3.—R. A. J., a 23-day-old white female infant, was admitted to the St. Louis Children's Hospital on Nov. 9, 1953. The infant was full term, weighing 8 pounds ½ ounce at birth. She was noted to choke and cough on feedings since birth. Several formula

changes were tried without improvement. Physical examination revealed a somewhat poorly nourished infant, weighing 7 pounds 5 ounces. The lung fields were relatively clear. The abdomen was considerably distended. When she was offered a feeding of sterile water, she would eagerly suck once or twice, stop, gag, choke and cough, taking thirty or forty seconds to recover. This sequence of events would be repeated when she was again offered water. A gavage tube could be easily passed into the stomach, thus ruling out esophageal atresia. A catheter could be easily passed through each nostril, thus eliminating the possibility of choanal atresia. It was felt that this patient had a tracheo-esophageal fistula, and x-rays were taken in an attempt to demonstrate it. A tube was inserted into the upper esophagus and 30 per. cent Urokon instilled. The esophagus was well-filled revealing no constriction or stenosis. During the procedure the patient questionably aspirated, and the films showed good bronchograms. X-rays taken in the lateral position did not reveal a fistulous tract. Later the infant was given Urokon to drink per bottle. Both an esophagogram and a bronchogram were obtained, but the x-rays again failed to demonstrate the fistula, and one could not definitely rule out the possibility that the Urokon was regurgitated and aspirated into the tracheobronchial tree via the larynx. On November 12 the patient was anesthetized with endotracheal cyclopropane, ether, and oxygen. With the patient in a supine position a small Mosher esophagoscope was inserted into the upper end of the esophagus. The endotracheal tube was withdrawn slowly until its end was just below the cords. Than a small polyethylene tube was inserted into the endotracheal tube, and 30 per cent Urokon tinged with methylene blue was instilled into the polyethylene tube while the operator carefully observed the esophagus through the esophagoscope. Immediately after the Urokon-methylene blue mixture was instilled into the trachea, there was a sudden gush of this material into the esophagus anteriorly, distal to the esophagoscope at a level about one-half the distance from the larynx to the bifurcation of the trachea. Three additional small injections were made with the same result. Spot films were taken during the procedure, but they failed to demonstrate the fistula.

The infant was fed by polyethylene nasogastric tube without incident while awaiting chest surgery. On November 18, under endotracheal anesthesia, the superior mediastinum was explored, and high above the cupola of the chest a small tracheo-esophageal fistula was found. The tracheal end of the fistula was closed with one layer of silk. The esophageal end was closed in two layers, and a mass of mediastinal fat was inserted between the two suture lines. The postoperative course was uneventful, and the infant was discharged on the twenty-first postoperative day.

DISCUSSION

These three cases exhibit the diagnostic pitfalls that beset one in attempting to make a definite diagnosis of tracheo-esophageal fistula without atresia of the esophagus. Although the diagnosis was strongly suspected clinically in Case 1, radiologic and endoscopic techniques were not sufficiently advanced to establish the diagnosis. It is doubtful if surgical skill ten years ago was such that successful closure of the fistula would have been possible. In Cases 2 and 3, several endoscopic and radiologic procedures were employed without successfully demonstrating the fistula. When Lipiodol was used as the contrast medium in performing the esophagogram, the oil seemed to be too viscous to pass through the small fistulous opening. When Urokon was substituted in the esophagogram in Cases 2 and 3, the medium was seen in both the esophagus and

the tracheobronchial tree, but no definite fistula was seen on any of the films. The possiblity of regurgitation and subsequent aspiration into the trachea via the supraglottic route could not be ruled out in that procedure.

The method used successfully in the latter two cases and described above has several advantages:

1. Endotracheal anesthesia gives the endoscopist a relaxed patient and one in whom the respirations can be controlled at all times. The danger of aspiration is greatly minimized.

2. The snug-fitting endotracheal tube and esophagoscope comprise an essentially closed system. The possibility of regurgitation of material from the trachea into the esophagus by the supraglottic route is minimized. If the media is placed in the trachea and then appears in the esophagus, it must by necessity have passed through a fistula.

3. The methylene blue saline solution can be readily seen and has such a low viscosity that it flows through the smallest fistula. The supine position of the patient permits gravity to aid the flow of solution from trachea to esophagus.

4. With repeat injections of dye, the endoscopist can move the esophagoscope to the exact level of the fistula. Lateral x-ray of the chest taken at that time will localize the level of the fistula. It is of considerable importance to the thoracic surgeon to know if the fistula is at the carina or some distance proximal to that point.

SUMMARY

Three infants with tracheo-esophageal fistula without atresia of the esophagus have been presented. The incidence, anatomy, symptomatology, and pitfalls in establishing this diagnosis have been discussed. An essentially closed system utilizing an endotracheal tube and esophagoscope with intratracheal instillation of dye and radiopaque media has been successfully used in two infants to establish the presence of a fistula and to localize it sufficiently to proceed with surgical closure.

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CONGENITAL SPINAL DERMAL SINUSES

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CONGENITAL dermal sinuses do not occur commonly in pediatric practice but when they do occur they all too frequently are not recognized in spite of the chronicity or recurrence of symptoms which they may produce; hence their recognition cannot be overemphasized. These lesions may be discovered in the course of a routine examination of the infant or child; or may be deliberately sought in a case of meningitis or one presenting neurological disorders of the legs or control of the sphincters. It is the purpose of this communication to describe the spinal congenital dermal sinuses, their clinical characteristics and treatment, and to present nine illustrative case reports.

The term "dermal sinus" covers a group of dysembryonic malformations comprising a tract from the skin overlying the spine extending inward to varying depths. The sinus is a dermal tube lined by stratified squamous epithelium opening onto the skin. In the walls of the tract or in associated cysts all the layers of the skin may be present, as may also be sweat and sebaceous glands, hair follicles and their products. Present terminology somewhat confuses anatomy and pathology, but it is permissable to refer to the whole group as dermal sinuses. When the tract is superficial to the sacral fascia and contains hairs, it is conventionally termed pilonidal sinus; if occurring at a deeper level, either attached to (Case J. V.), or communicating with, the dura (Cases J. DeV. and R. B.), it is a dermal sinus; and at any depth, either subcutaneous (Case J. V.) or in the spinal cord itself (Case C. C.), epidermoid or dermoid cysts may be present. Epidermoids contain only the epidermal layers of the skin; dermoids may consist of all layers including the accessory cutaneous organs.

Pilonidal sinuses, although probably present from birth, rarely manifest themselves before adult life and may, in fact, be the result of repeated trauma in individuals who are in some way predisposed to the condition. A communication with the spinal canal is most unusual and, therefore, although painful and annoying to its possessor, a pilonidal sinus is unlikely to be accompanied by the dangers to neurological function and even to life which make the other types of dermal sinus so important. They will not be further discussed here.

The embryological defect, according to Critchley and Ferguson[1] and Walker and Bucy,[6] occurs in early fetal life at the period of differentiation of ectoblast into cutaneous and neural ectoderm. As the neural groove closes, forming the medullary tube, cutaneous ectodermal cells may also be invaginated, subsequently developing into intraspinal dermoid or epi-

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dermoid growths. When there is a related defect of mesodermal organization in the same region, the tract is associated with a bony abnormality, a spina bifida, and may connect the skin directly to the contents of the spinal canal. Or the anomaly may be still more superficial, consisting of a failure of completion of fusion of cutaneous ectoderm after this has separated satisfactorily from the neural ectoderm. Fusion at this level commences at the middle of the embryo, the caudal and cranial ends completing the process. This seems a reasonable explanation for the prevalence of these lesions, first in the lumbosacral region and next in the suboccipital region, and of their rarity in between.

Clinically, they are encountered either as a result of routine examination of an otherwise normal child, because of local infection or of meningitis, or in the investigation of spinal neurological disorder. The sinus usually opens on the surface in or near the midline in the lumbosacral region, but it may be found at any point along the spinal axis. The point is small and may be apparent only with the aid of a magnifying lens. The adjacent skin may be normal in appearance and on palpation, but frequently a flat, cutaneous hemangioma surrounds the opening and there may be a localized hypertrichosis. Even in the absence of previous infection, subcutaneous thickening or a small lipoma may be present, and on moving the skin the appearance of a dimple suggests tethering to deeper structures. On occasions there may be intermittent discharge from the sinus with no evidence of frank infection. Radiographic examination may demonstrate the presence of an associated spina bifida or other spinal abnormality. Local infection of the sinus tract and adjacent tissues by *Bacterium coli* or staphylococcus with abscess formation is common. The history may indicate the occurrence of many such abscesses which spontaneously discharged, with long intervals during which the lesion was forgotten. However, as a primary episode, or after bouts of local infection, an attack of meningitis may develop, probably with some pyogenic organism. Or there may have been one or more previous attacks of meningitis before the source of the infections is traced to a possibly inconspicuous lesion on the back.

The nature of the infecting organisms, the possibility of their resistance to antibiotic therapy, and the persistence of an infected focus in communication with the spinal canal emphasize the importance of recognizing these abnormalities as potentially lethal. Therefore, when the clinical appearances make the diagnosis of dermal sinus reasonably certain, surgical excision of the sinus tract should be undertaken as a prophylactic measure. Under these circumstances myelography is an unnecessary investigation and the injection of dye into the tract is probably inadvisable. Local infection or meningitis in the absence of progressing neurological abnormality should first be treated with suitable antibiotic or chemotherapeutic agents before the tract is formally excised, although incision of a superficial abscess may be indicated.

Neurological signs and symptoms in this condition are due to increasing volume, and/or infection, of the intraspinal portion of the sinus. The symptoms may be intermittent or of grad-

ual onset over a long period and are then probably due to the accumulation of secretory products of an intraspinal cyst—remissions following discharge of part of this material. Or the onset may be swift and accompanied by constitutional or meningeal signs, suggesting the development of extradural, subdural, or intraspinal abscess or the thrombosis of spinal blood vessels. A distant complication of a firmly adherent, infected, intraspinal dermal cyst—distant both in time and space—could be the development of the Arnold-Chiari malformation. Likewise the fixation of the distal end of the spinal cord, by a tract or by adhesions, may lead to neurological disturbance in that region. Whether of gradual or of sudden onset, the patient may present the picture of spinal cord compression, nerve root irritation, or the cauda equina syndrome, depending on the level of the lesion. Pain in the back or legs is usual with abscess formation, or with meningitis due to rupture of the irritating contents of a dermoid cyst. Motor weakness to the extent of paraplegia, with appropriate reflex changes, is seen, and in the chronic cases equinus deformities of the feet occur. Sphincter disturbances of various degrees are often present and in the long-standing cases may take the form of an obstinate constipation. With significant spinal cord involvement it is usually possible, even in children, to demonstrate a level of sensory impairment. The observation of associated autonomic changes, resulting in decreased sweating, can be employed in infants to provide confirmatory evidence of the level of spinal cord damage. This level may be determined by passing the dry hand lightly over the skin, when one can often feel the level of presence or absence of sweating. Additional information may be obtained by the starch and iodine test for perspiration. The development of progressive loss of neurological function is an indication for immediate surgical exploration under adequate antibiotic therapy to decompress neurological structures and to remove infected tissue and material as found practicable.

Myelography is not employed when the nature of the lesion is suggested by the abnormality of the skin and superficial tissues. In the more chronic cases, such as a spinal or paraspinal dermoid cyst without cutaneous abnormalities, myelography would be indicated as in the diagnosis of any suspected spinal tumor.

Operation is by laminectomy, an elliptical skin incision enclosing the sinus opening and any abnormal skin surrounding it. The tract is dissected through the fascia to the dura which should be opened for a short distance around the attachment of the tract to enable any intradural extension to be dealt with. Usually the tract ends blindly just deep to the dura at a point higher than the position of the dimple. Intradural cysts are completely removed without opening if this is possible and does not endanger nervous elements. Intraspinal and adherent intradural cysts are emptied of their contents and as much capsule as possible removed. Attempts to remove the hard, fibrous capsule of an infected intraspinal cyst are fruitless and lead to additional and avoidable loss of function. A watertight closure of the dura is made and the muscles and skin are closely approximated

without drainage. Drainage of an extradural abscess after operation may be necessary.

CASE REPORTS

CASE 1.—V. B., was first seen in November, 1948, at the age of 2 years. The complaint at that time was of difficulty with bowel movements and urination since birth; also difficulty with walking on first rising in the morning. There had apparently never been complete bladder control, although she did not wet the bed at night. One week before admission a pigmented area over the lower lumbar region of the back became swollen and tender.

The child had been born by cesarean section because of maternal bleeding and was placed in oxygen after delivery, but was apparently normal and subsequently developed normally. The birth weight was 5 pounds 5 ounces. She sat at 8 months, walked at 14 months, and in other respects progressed satisfactorily, apart from the sphincter difficulty and the difficulty with walking first thing in the morning. On examination, there was no fever and the child appeared well and adequately nourished. There was a small, slightly inflamed nevus in the midline of the back overlying the spine of the fourth lumbar vertebra. The nevus measured 1.5 by 2 cm. and the center was depressed, from which area several silky hairs protruded. At a lower level there was a small dimple over the first sacral spine. Rectal examination revealed fairly good sphincter tone but there were considerable feces in the rectum. Intravenous pyelogram was normal and residual urine was less than 5 c.c. Other blood and urine examinations were normal. X-ray of the spine failed to reveal a spina bifida and the bony structure was normally developed. A dermal sinus was excised in November, 1948. The patient's progress was followed until May, 1950. When last seen she had complete bladder and bowel control. The deep reflexes were increased on the left and the adductors of the thigh were thought to be tighter than normal. The plantar responses were flexor. The child was healthy and was developing normally.

CASE 2.—J. B. was admitted to the hospital in August, 1948, with a complaint of fever for seven days and a stiff neck for two days. He had previously been admitted to another hospital on two occasions within the preceding month with a diagnosis of meningitis. His birth history and early development were normal and he had been quite well until two months before admission to the hospital.

However, a "dimple," at the base of the spine, had been observed since birth, but this had not discharged until May, 1948, when a small quantity of yellow pus was noted. This discharge continued intermittently for the next two months. On the first occasion when the sinus discharged pus, the child vomited on the same day and had a temperature of 102° F. Four days later he was admitted to the hospital and lumbar puncture revealed a cloudy fluid under increased pressure containing 1,500 cells, predominantly polymorphonuclear cells, but no organism was grown on culture. He was treated with penicillin, streptomycin, and sulfadiazine and made steady progress. On discharge, two weeks later, he appeared to be quite normal. Immediately before discharge, further cerebral spinal fluid examination showed a cell count of 62 white cells, predominately polymorphonuclears, and culture was again negative.

He had, however, been at home only two days when the meningitis recurred. His condition on readmission was essentially as before. The cerebral spinal fluid now showed a cell count of 1,300 and he was again treated with penicillin, streptomycin, and sulfadiazine. On this occasion there was not the previous rapid improvement, and at the end of six days of treatment the temperature still remained elevated. Lumbar puncture

showed 900 white cells, almost equally divided into lymphocytes and polymorphonuclear cells. He was transferred to the Children's Memorial Hospital with a diagnosis of suspected intracranial abscess.

Lumbar puncture on admission yielded a slightly cloudy fluid under normal pressure containing 638 white cells, predominantly polymorphonuclear. No organisms were seen on smear but anaerobic culture produced growth of gram-negative pleomorphic bacilli showing bipolar staining. While he was in the hospital, the sinus and the lumbar region continued to discharge a fine serous fluid, but no abnormal neurological signs developed. The meningitis persisted, with abnormal cerebral spinal fluid constituents being recorded on three occasions. He slowly improved and was returned to the original hospital for continuation of the treatment for the meningitis and surgical treatment was arranged there. Two weeks after discharge from this hospital, operation was performed at the Butterworth Hospital, Grand Rapids, by Dr. List who found and removed a dermal sinus between the fifth lumbar and the first sacral vertebrae. The sinus extended extradurally and ended as an intra-arachnoid dermoid of tubular character at the level of the third lumbar vertebra. There was no epidural or subdural abscess but some arachnoiditis of the caudal roots. The patient made an excellent recovery and has since developed normally.

CASE 3.—R. B. was admitted for treatment of a discharging sinus which was situated over the fifth lumbar vertebra in the midline of the back. The child was 11 months old and had developed normally. The birth weight was 6 pounds 12 ounces, and on admission the weight was 17 pounds 7 ounces. He sat at 6 months but could not yet stand alone. The sinus had been present since birth and had drained yellow purulent material intermittently about twice a month since birth, the drainage lasting on each occasion about one day. On the back there was an area 1 inch in diameter, just to the left of the midline, consisting of a hemangioma surrounded by coarse hair. In the center of this area, there was a depressed region, but no actual opening or exudate could be seen. The neurological examination was negative. Operation was undertaken soon after admission and the abnormal skin was excised. The sinus was dissected down to the lamina and after removal of a small amount of bone, was followed to the dura. It was excised at the dural level and a small quantity of spinal fluid flowed from the opening in the dura which was then closed with a stitch. The wound was closed in layers and healed satisfactorily. Pathological examination showed the sinus to be lined with essentially normal, stratified, squamous epithelium, but the dimple of the skin surface did not admit a probe. Beneath the epithelium there was dense connective tissue, and at one point within this tissue there was an irregular space lined with loose vascular tissue, with no definite lining. The specimen was diagnosed as a neurodermal sinus. The child was discharged from the hospital a week after the operation, apparently well, and there have been no further visits to the hospital.

CASE 4.—M. M. was admitted to the hospital at the age of 2½ months with a history of normal birth and development until three weeks previously, when there was a sudden onset of urinary dribbling and flaccidity of the legs. Soon afterward severe constipation was noted for the first time. On examination at the time of her admission, the legs were flaccid and limp, although the child could flex the legs at the thighs and adduct them slightly. There was a constant dribbling of urine. Knee and ankle jerks were absent, and on digital testing of sweating, the skin seemed to be completely dry below the level of the D 2 dermatome. The signs suggested a transverse lesion at the level of D 2 or L1. This was thought probably to be a spinal cord neoplasm.

On further examination, however, a small hemangioma, measuring 1 by 0.5 by 0.3 cm., was seen at the level of the fifth lumbar spine posteriorly. Pressure on this area produced a drop of yellow fluid from a tiny sinus opening at the center of the nevus. Three days after admission there had been some improvement in the child's neurological condition. The sensory level was at L5 with only a saddle region of hypalgesia. There was some voluntary movement of both legs, although this was not normal. The rectal mucosa was slightly prolapsed. There had been a slight discharge from the dermal sinus during the previous twenty-four hours. As the sensory level was lower than it had been on admission and the child's general condition appeared to be improving, treatment was continued with sulfathiazole, and although the temperature ranged from 101° to 103° F. for four days, it was then normal for two days, when the child was transferred to another hospital for surgical treatment.

At operation the hemangiomatous area of skin was excised by an elliptical incision and a white stalk of tissue was traced to the vertebral canal where it appeared to be continuous with the spinal cord. A probe passed from the external stoma was felt to fall into the substance of this strand of white tissue, which was followed along the vertebral canal for 4 cm. It was impossible to distinguish the cauda equina, but nerve roots were seen to pass from the mass on each side. The obviously cutaneous part of the mass was excised and the remainder returned to the canal.

Pathological Report.—The tube was lined by normal stratified epithelium; sebaceous glands and hair follicles were present. There was no inflammatory reaction. *Diagnosis.* Congenital dermal sinus. There was a smooth postoperative convalescence, and on discharge from hospital the child's legs had recovered practically normal power and there were no abnormal neurological signs. Four months later the hospital was informed that the child, who was now living in a distant city, had had an attack of meningitis. This was successfully treated with sulfathiazole and the child's condition was again fairly good, although he was much troubled by constipation. Bladder control was said to be satisfactory. The operative wound was well healed and there had been no local signs of inflammation at the time of the meningitis. He was making good progress at the age of 2 years but nothing further has been heard from the family for ten years.

CASE 5.—M. R. first entered the hospital at the age of one year with a complaint of spasticity of the right leg and with a flaccid paralysis of the left leg. There was a level of hypalgesia below D6 and a small nevus with a central draining sinus at the level of L2. X-rays showed a spina bifida occulta and a diagnosis of congenital dermal sinus with myelodysplasia was made.

She was then readmitted in April, 1948, two years after the first admission, with symptoms of meningitis. Lumbar puncture at that time yielded a slightly cloudy fluid containing many polymorphonuclear cells which grew a *Hemophilus influenzae.* She was treated with sulfadiazine and streptomycin. But at this time she was found to be suffering from a hydronephrosis, had loss of sphincter control, and a chronic pyuria developed. The meningitis was controlled by chemotherapy, but the child remained in poor health for the next two years, when she was again admitted with a recurrence of meningitis and purulent discharge from the spinal dermal sinus. On this occasion she was treated with penicillin, sulfadiazine, and streptomycin, and although lumbar punctures were not successful, blood cultures at this time grew *H. influenzae.* In March, 1950, operation was performed for removal of the dermal sinus. A laminectomy was performed on the fourth and fifth lumbar segments. The sinus extended down to the dura as a narrow stalk which measured about 1.5 mm. in diameter.

Beneath the first sacral arch there was a marked expansion of the dural tube. The laminae of the fourth and fifth bodies were intact and the sinus entered the dura between the fifth lumbar lamina and the first sacral lamina. The stalk was cut off at the level of the spinous process. A drop of pus had exuded from the opening of the dermal sinus. The laminae of the fourth and fifth bodies were then removed and uncovered normal dura. Because of the presence of infection in the dermal sinus the dura was not opened. There was no recurrence of meningitis, but the patient entered the hospital for the last time three months later and died on June 23, 1950. The post-mortem examination revealed an extensive lesion of the spinal cord extending from the level of the seventh thoracic segment caudally to the conus medullaris. Almost one-half of the spinal cord showed degenerative changes associated with chronic inflammation. The overlying meninges were thickened, fibrous, and infiltrated with lymphocytes and monocytes. In places this fibrous tissue appeared to invade the cord. In the lower levels of the cord almost its entire thickness was involved. Examination of the brain also revealed signs of meningitis. The cause of death was given as bilateral hydronephrosis and hydroureter with severe cystitis, the urinary infection being secondary to degenerative spinal cord disease. The attacks of meningitis and possibly the spinal cord damage could be associated with infection from the spinal dermal sinus.

CASE 6.—C. C. was admitted to the hospital at the age of 10 months because of a painful, draining swelling over the lower spine for three months, and loss of power in the legs for one month. At birth, it was noted that there was a hemangiomatous area, about 1 cm. in diameter, in the lower lumbar region, in the midline; several hairs grew from a central dimple. In December, 1952, the hemangiomatous area became inflamed, swollen, and tender, and she had a raised temperature. The local doctor then incised the swelling and there was much purulent discharge. Penicillin was prescribed and her general condition improved. However, early in February, 1953, the parents noticed that the child did not use her legs and she was admitted to the hospital on March 30, 1953. The lower extremities were flaccid and there was only a little movement in the hips. The rectal sphincters were relaxed and the mucous membrane a little prolapsed. There was no response to painful stimuli below a sensory level at the lower chest. In the lumbar region there was an abscess at the site of the hemangiomatous area. It was thought that the infection from the abscess, probably associated with a dermal

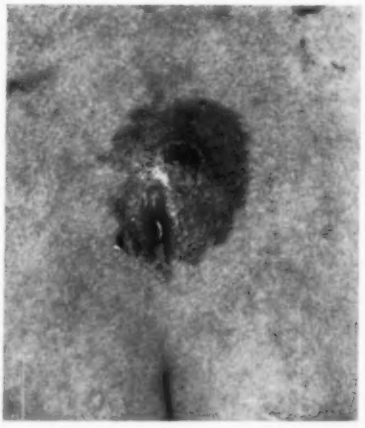

Fig. 1.—C. C. Dermal sinus of lower lumbar region with hemangioma noticed at birth. Dermal sinus is in lower midline with healing area of infection above.

sinus, had caused thrombosis of spinal vessels, or that there was an intraspinal abscess. She was treated with penicillin and sulfonamides, and three days after admission the abscess was incised with the drainage of 5 c.c. of yellow pus. After this there was thought to be some slight improvement in the movements of the legs, the drainage continuing on and off.

Operation was undertaken ten days later. The sinus passed through

Fig. 2.—Myelodysplasia with paralytic and sensory changes in lower extremities due to infection along tract of a dermal sinus extending into lower lumbar cord.

Fig. 4.—C. C. Post-surgery; moderate recovery of paralytic changes in lower extremities.

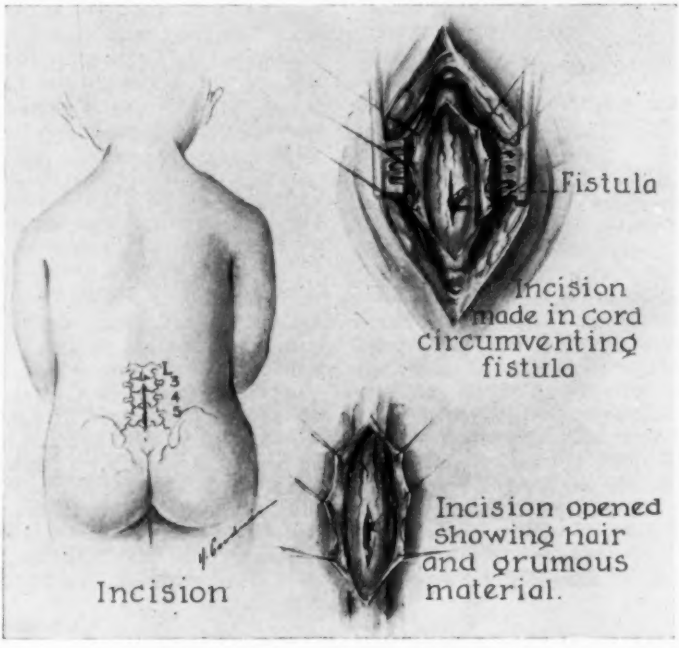

Fig. 3.—C. C. Diagrammatic pathology of dermal sinus extending into lumbar region.

bony defect at the lumbosacral junction. The lower three lumbar spines and laminae were removed and the sinus was followed into the dural sac, the dura being opened upward from the point of attachment to the sinus for a distance of 4 cm. The sinus entered the cord 2 cm. above the lower end of the conus medullaris which was firm and swollen and unusually pale, with few vessels on the surface. There was no pulsation, nor was there escape of cerebrospinal fluid. Evidently the subarachnoid space was obliterated. The neck of the sinus at its entrance in the cord was enlarged and 3 c.c. of creamy fluid under pressure issued from the cord. The cord was incised for 1 cm. upward from the sinus, thus exposing a dermoid cyst 3 cm. in length and almost 1 cm. in diameter,

Fig. 5.—Postoperative area in lumbar region; hemangioma still present but dermal sinus has been excised.

which contained epithelial material and a few hairs. The wall of the cyst was hard and irregular and it was not possible to separate it from the spinal cord. After cleaning out all debris with warm saline, the wound was closed in layers. The child made a satisfactory recovery and the wound healed well with no further discharge. She has been followed in the outpatient clinic for eighteen months. There is good bladder control but the rectal sphincter is weak, which causes little difficulty as the child is constipated. There is some power in the proximal muscles of the legs, and recently there appears to be slight improvement in the more distal groups since the child is now able to stand with assistance. Orthopedic care is being arranged and her prognosis may be better than was initially expected.

CASE 7.—J. D. was admitted to the hospital on the eighth day of life because of a small area of abnormal skin in the lower lumbar region which was slightly swollen and inflamed and which had been present since birth. The child was 5 pounds at birth and had made fairly good progress, being 5 pounds 10 ounces when admitted to the hospital. However, it was thought advisable to delay the operation until she had developed further. She was readmitted at 3 months of age and had developed well in the interval. There were no neurological abnormalities; the legs moved normally and the sphincters appeared unimpaired.

On May 26, 1953, operation was undertaken for the excision of the dermal sinus. The skin was excised surrounding the sinus in an elliptical manner and a 3 mm. diameter dermal sinus was followed down to the dura by a small laminectomy exposure. The dura was normal except for one large artery on the surface and no abnormalities were palpable in the dural sac. The tract was opened and cerebral spinal fluid ran out. The connection of the sinus to the dura was closed with a silk stitch and the sinus excised. The wound was closed in layers.

The child recovered satisfactorily and subsequently did well except for a small granulating area in the wound which healed only after the removal of two silk sutures. She had since remained well without complications.

CASE 8.—J. V. was admitted to the hospital at the age of 2 years for the removal of a small mass 3 cm. in diameter which was present in the lumbosacral area since birth. He was otherwise a normal child, walked well, and had good sphincter control. There were no neurological abnormalities. The swelling in the midline of the lumbosacral region was thought to be a lipoma and the skin overlying it showed hemangiomatous changes.

On March 16, 1954, operation was undertaken for removal of a lipoma. An elliptical incision was made and the fatty tissue was dissected through the deep fascia and continued following a sinus tract 5 mm. in diameter. This was followed to the dura by a small laminectomy. The tract was then ligated at the dural attachment and excised. The dura appeared normal on inspection and palpation. The wound was closed in layers.

Pathological report by Dr. Joseph D. Boggs was as follows:

Gross Description: Specimen consisted of an elliptical wedge of skin and subcutanoeus tissue measuring 4.0 by 3.0 by 1.0 cm. The skin surface showed purplish mottling. Cut sections revealed the subcutaneous tissues to be the seat of a lined, empty space approximately the size of a pea. The lining was pale white in color.

Microscopic Examination: Sections revealed a block of tissue lined on one side by normal-appearing, stratified squamous epithelium of the epidermal type. No abnormalities of this epithelial layer were apparent. In the subepithelial tissues several sweat glands were identified and an occasional hair follicle without hairs. There was an increased amount of collagenous connective tissue. There was no evidence of inflammatory alteration. No discrete layer of cells was seen to line this space but an occasional group of flattened cells were present, suggesting a mesothelium. There was no evidence of neural tissue in or around this structure.

Diagnosis: Skin and subcutaneous tissues. Subcutaneous cyst.

The child has since been well and there have been no further complications.

Case 9.—V. J., 2 weeks of age, was admitted to the hospital because of a swelling in the lower lumbar region ½ cm. in diameter which occasionally discharged purulent material. Around the edges of the swelling were three small hemangiomatous areas. X-rays showed no spinal defects. The child otherwise appeared normal, moved her legs normally, and had good rectal sphincter contraction. There was evidently also bladder control as the diapers were dry at times. She was treated for the sinus until the infection disappeared, and operation was undertaken on Jan. 26, 1954. A transverse elliptical incision enclosing the sinus was made and the neck was dissected to a defect in the deep fascia about 5 mm. in diameter. This was then enlarged and a small central portion of the lamina of L5 was removed. The sinus constantly decreased in size until where it was attached to the dura it was a cord no more than 2 mm. in diameter. A ligature was then tied flush with the dura and the sinus excised. There appeared to be no lumen to the sinus at its dural attachment. The child made a satisfactory recovery and has been well since, with no neurological complications or any discharge from the wound.

Pathological report by Dr. Joseph D. Boggs is as follows:

Gross Description: Specimen consisted of an elliptical wedge of pale, hairless skin and subadjacent tissue measuring 4 by 1.5 by 0.5 cm. In the center of the specimen was a circular elevation approximately 1 cm. in diameter. From this area a narrow stalk of whitish tissue was seen to extend through the specimen. Surrounding this was a diffuse, well-circumscribed amount of soft, mucoid grayish tissue.

Microscopic Examination: Sections revealed a mound of skin and subcutaneous tissue. In the center of this mound was seen a small punctum. The epidermis revealed a moderate degree of blunting of the rete pegs. The stratum corneum was thin. The stratum spinosum was markedly hyperplastic and the malpighian layer was relatively thin and inactive. The punctum previously mentioned was seen to be a thin cleftlike space lined by the same epithelium as the epidermis. It was seen to project into a corium which was the seat of marked pathologic alterations. The corium

appeared to be replaced by vascular, mature granulation tissue arranged in septa. Between these septa could be seen large areas of myxomatous tissue. Several foci of acute and fibrinoid necrosis could be seen. These were small and well circumscribed.

Diagnosis: Dermal sinus, the seat of granulomatous, myxomatous alteration, and acute necrosis.

SUMMARY

The embryology of the defects in congenital spinal dermal sinuses is discussed and the clinical manifestations and management are described.

The case histories of nine patients with this condition are presented.

The recognition of congenital spinal dermal sinuses is of the utmost importance. The visible part of the lesion may be insignificant but the presence of the sinus may be betrayed by a dimple, a small hemangiomatous area, or by hypertrichosis in the midline of the back.

Infection of the central nervous system via such a sinus may result in recurrent attacks of meningitis or in localized damage to the spinal cord.

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THE TREATMENT OF PINWORM INFECTION (ENTEROBIASIS) WITH GENTIAN VIOLET SUSPENSION

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THE value of methylrosaniline (gentian violet) as an oxyuricide has been adequately established. D'Antoni and Sawitz,[1] using enteric-coated gentian violet tablets orally in the treatment of enterobiasis, have reported a 90 per cent cure rate. Miller and co-workers[2] have likewise reported a 90 per cent cure rate with enteric-coated gentian violet tablets. Eighty-two per cent of forty infected children treated with enteric-coated gentian violet tablets were reported cured by the authors.[3] Allen[4] reports a cure rate of 97 per cent with the combined treatment of oral gentian violet tablets and gentian violet suppositories made of gentian violet 0.25 per cent and benzocaine 2 per cent in a polyethylene glycol base.

While the rate of cure with gentian violet is sufficiently high to make it a satisfactory oxyuricide, many children, particularly the younger ones, are unable to swallow the intact enteric-coated gentian violet tablets. Attempts to administer the tablets, broken into several smaller pieces, invariably cause nausea and vomiting. In view of these observations, many clinicians have expressed the opinion that a palatable and well-tolerated solution of gentian violet would dispel this one serious disadvantage in the treatment of pinworm infection with gentian violet.

Solutions of gentian violet, compounded by local pharmacists, have been used in the treatment of enterobiasis by some clinicians.* However, in almost all instances, these solutions have proved to be irritating to the gastric mucosa and frequently result in nausea and vomiting. A phenolphthalein salt suspension of gentian violet, which produced no evidence of gastrointestinal irritation in test animals, proved equally unsatisfactory when we treated a group of children infected with pinworms. While the treated children took this palatable suspension without complaint, almost all of them shortly after taking it became nauseated and vomited. It was thought that this reaction was caused by the dissociation of the gentian violet from the phenolphthalein salt. On this basis a new suspension employing the phenolphthalein salt of gentian violet, which was held in an insoluble complex by an inert earth, was used. Evidently this preparation did not break up so readily in the stomach and did not result in nausea and

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*Personal communication.

vomiting. The object of this paper is to report on the results obtained in treating pinworm-infected children with this new suspension.*

CLINICAL MATERIAL AND METHOD

Twenty-six children infected with *Enterobius vermicularis* were treated with a gentian violet suspension at the Immaculate Heart of Mary Home as an outpatient project of the Edward J. Meyer Memorial Hospital in Buffalo, New York. The children, fifteen males and eleven females, ranged in age from 5 to 13 years. The diagnosis was established by the use of a modification of the Graham Scotch tape swab technique which we have described in detail in an earlier publication.[5] Seven days after treatment, two Scotch tape swab smears were made daily for one week to determine the results of the treatment. Those patients whose smears were negative for the seven consecutive days were declared cured. In addition to the twenty-six infected children, fourteen other noninfected children, nine females and five males, ranging in ages from 3 to 16 years, were also treated with this same suspension of gentian violet. By treating these fourteen noninfected children of this group of forty children we hoped to minimize the possibility of allowing infected children who at that time may have had negative diagnostic smears to go untreated and thus possibly reinfect the treated children.

Without any previous preparation, all forty children received a suspension containing 6 mg. of gentian violet per cubic centimeter. The children aged 3 to 5 years received a level teaspoonful of the suspension twice daily for fourteen days. Those aged 6 to 10 years received one rounded teaspoonful three times daily for fourteen consecutive days, and those aged 11 to 16 years received one and one-half teaspoonfuls three times daily for fourteen consecutive days. On the basis that the maximum amount of gentian violet tolerated by children is 9 mg. ($\frac{3}{20}$ gr.) daily per year of apparent age, the youngest children who received a scant teaspoonful of the suspension (about 4 c.c.) twice daily received about 48 mg. of gentian violet or a little over the average dose. The children in the second group, aged 6 and 7 years, received one teaspoonful three times daily (about 90 mg. daily) or about one-third more than the average dose of gentian violet, and those aged 8 to 10 years received an average dose of gentian violet. Those children in the age group 11 to 16 years received slightly more than the average dose of gentian violet except the children 14 to 16 years old who received an average dose of the dye. The dose schedule was not calculated to the exact 9 mg. per year of apparent age because this would have added considerably to the chore of medicating so large a group of children, particularly since the complete study conducted at this home, and which will be reported at a later date, included all the 170 children of this home. In addition to the gentian violet suspension treatment, the usually recommended personal and environmental hygienic measures were adhered to as closely as possible.

*The suspension of gentian violet was supplied by Eli Lilly and Co., Indianapolis, Ind.

RESULTS AND DISCUSSION

Of the twenty-six infected children treated, twenty-one had two daily negative post-treatment Scotch tape smears for seven consecutive days. All these were declared cured. The remaining five patients had one to two positive post-treatment smears (Table I). The cure rate in this series of patients treated with the gentian violet suspension was 81 per cent. However, patient C. P. (Table I) had a positive smear on the first post-treatment day and negative smears on the following six consecutive days. Patient R. S. had positive smears on the second day and negative smears on the following five consecutive days. Patient J. D. had positive smears on the first two days and negative smears on the following five days. Since these three patients had five to six consecutive days of negative smears, it might reasonably be concluded that they too were cured but remained positive one to two days longer than the rest of the patients. If these three patients are included with the twenty-one cured patients, this would raise the number of cured patients to twenty-four, or a corrected cure rate of 92.3 per cent.

The gentian violet suspension which was taken undiluted from a spoon was well accepted and tolerated by all of the children. Some of the children preferred to mix the suspension in 1 to 2 ounces of water. The resulting mixture made a palatable drink that looked and tasted like grape juice. A few of the children preferred to drink 1 to 2 ounces of Concord grape juice immediately after taking the gentian violet. In no instances were any of the children upset by the medication. No nausea or emesis was encountered in any of the children. Sample post-treatment blood counts and urinalysis done on ten of the patients were normal.

The fourteen noninfected children remained negative following the same treatment that was given to the infected children. As in the infected group, no remarkable reaction was observed in this group of children.

TABLE I. FAILURES IN TREATMENT

PATIENT	AGE	POST-TREATMENT SMEARS						
		DAY 1	2	3	4	5	6	7
C. P.	9	+	−	−	−	−	−	−
R. S.	13	−	+	−	−	−	−	−
J. D.	12	+	+	−	−	−	−	−

SUMMARY

1. The percentage of cures in a series of twenty-six infected children treated with a suspension of gentian violet was 81 per cent. The corrected cure rate was 92.3 per cent.

2. The suspension of gentian violet was well accepted and tolerated by all forty of the children who received the medication in this study.

3. The nausea and vomiting observed in some patients treated with the enteric-coated gentian violet tablets was not observed in these patients treated with the suspension of gentian violet. Since the nausea and vomiting observed in patients treated with the enteric-coated gentian violet tablets, coupled with the inability of young children to swallow the intact enteric-coated tablets, comprise the major dis-

advantages in the treatment of enterobiasis with the enteric-coated gentian violet tablets, it appears from this study that the suspension of gentian violet is a more desirable method of treatment than the enteric-coated gentian violet tablets.

We express our appreciation to Mrs. Rose Krier for her technical assistance.

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Early Medical Advertising

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POSTURAL VERTIGO DUE TO TRIGGER AREAS IN THE STERNOCLEIDOMASTOID MUSCLE

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A CLINICAL syndrome characterized by postural vertigo or dizziness, imbalance, and usually headache may have its source in trigger areas in the sternocleidomastoid muscle. Recently a report of thirty-one adults with this condition was made,[1] which calls attention to our earlier references to this syndrome.[2, 3] It is our purpose in this paper to present the case history of an 11-year-old girl with this clinical picture, and to review the features and treatment of this condition.

Previously, several authors[4-10] have noted that musculoskeletal disorders of the head and neck may be accompanied by vertigo, but none of these attributed a specific role to the sternocleidomastoid muscle in the etiology of dizziness.

CASE REPORT

J. T., an 11-year-old girl, was first admitted to the New York Hospital on March 5, 1954. She had been well, except for febrile episodes of tonsillitis about twice yearly, until sixteen days prior to admission, when she suddenly felt very dizzy and staggered on rising from bed in the morning. "The room seemed to move." Vertigo was intensified by stooping, sitting, or lying down, and occurred also on turning over in bed. These episodes of vertigo lasted one to five minutes, and were not accompanied by aura, loss of consciousness, vomiting, deafness, or tinnitus. Headache was absent at this time. She remained in bed, took aspirin, 0.3 Gm. every four hours, without relief. On the following day, the postural vertigo was accompanied by headache, especially behind the eyes while studying.

She was seen by her private physician. At this time she showed mild leukopenia and a slight tendency to myopia; glasses were not thought necessary.

The following week the patient had dizzy spells less frequently and was able to get up. One week prior to her first hospital admission she had disequilibration without vertigo. She said that she tried to turn one way and was surprised to find that she veered toward the other side. The following day the attacks of vertigo returned. At this time skull x-rays and an electroencephalogram were negative. On the day before hospitalization, imbalance was intensified and she developed a constant headache of dull, squeezing, or boring quality, which became worse when she sat up. During the last two days before admission she fell twice, and she tended to veer somewhat to the right on walking. Therefore, she was admitted to the hospital.

There was no history of recent head trauma, toxic ingestants, or infectious illness. Five years earlier she fell down a flight of steps and required stitches in the scalp in the occipital region.

Family History.—This was noncontributory except that the maternal grandmother had epileptic attacks at

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an advanced age. Her mother was subject to acute stiff neck and other myalgias.

Past History.—Prenatal course was normal, birth uneventful at term. Infancy and childhood were normal. The patient had mumps at 5 years, measles at 7 years and pertussis at 10 years, all without complications or sequelae. She was subject to attacks of tonsillitis. She was susceptible to motion sickness, a tendency which had been less pronounced in the past year.

Physical Examination.—The patient was a well-developed, alert, and intelligent white girl of 11 years. She did not appear acutely ill. During the initial examination, when she sat up she had severe dizziness which lasted five seconds. Nystagmus was not present during postural vertigo. Pulse rate was 96 per minute, blood pressure 115/72 mm. Hg, respiratory rate 16 per minute, and oral temperature 37.0° C. Skin and hair distribution were normal. Head was normocephalic, with slight occipital protuberance; no bruit was heard. Face was symmetrical. Pupils were normal. Extraocular movements were performed well without nystagmus. Corneas and scleras were clear. Fundi were normal. Visual fields were grossly normal. Tympanic membranes and external auditory canals were normal. Hearing was grossly normal. Nasal mucosa was not congested. Extensive caries were present in the deciduous teeth. Tonsils were cryptic and large. There was no lymphadenopathy. Thyroid gland was not enlarged. Motion of the neck was not restricted. Chest was symmetrical, with early breast development. Lungs were clear. Heart showed regular sinus rhythm, normal heart sounds, and no murmurs. Abdomen was soft with the liver edge just palpable at the right costal margin; otherwise examination of the abdomen was negative. External genitals were normal. Extremities revealed no deformities or limitation of motion; pulses were readily palpable.

Examination of the nervous system showed an oriented, alert, cooperative girl of above-average intelligence. She expressed normal concern about her condition. The gait was a slow walk, and the patient braced herself against the wall for fear of falling. When she tried to walk a straight line, she intermittently veered to the right. Cranial nerves were intact. Perception of pinprick and light touch was normal. Tests of motor function were normal, without muscle atrophy, weakness, or adventitious movements. Cerebellar functional tests were performed well, including the Romberg, finger-to-nose, heel-to-knee and shin, and rapid alternating coordinated movements. Superficial and deep tendon reflexes were normal.

Laboratory Findings.—Urinalysis was unremarkable. The blood count showed hemoglobin 14 grams, erythrocytes 4.8 million, white blood cells 5,900 with a normal differential count. Blood chemistry showed urea nitrogen 12 mg. per cent; serum electrolytes normal. The tuberculin test was negative (1 to 10,000). Excretion of the 17-ketosteroids was 4.5 mg. per twenty-four hours (urine volume 485 c.c. per twenty-four hours).

X-ray examination showed the skull to be normal. X-rays of the sinuses, petrous pyramids and mastoid bones revealed no abnormality, except that the left mastoid region appeared less aerated than the right; there was no evidence of cholesteatoma or active infection.

Nose and throat cultures disclosed no pathogenic organisms.

Audiograms recorded on March 9 and 11, 1954, were normal. The Weber test was not lateralized (normal).

The ice-water caloric test performed on March 12, 1954, by Dr. James Moore was normal. There was no prior spontaneous nystagmus. Rotatory nystagmus for the right ear

appeared in 25 seconds, duration 125 seconds, and for the left ear, in 24 seconds, duration 121 seconds. Dizziness, past-pointing, and falling to the appropriate side also developed.

Perimetry on March 12 showed the visual fields to be normal; visual acuity was 20-20 for both eyes. The ophthalmologic consultant reported: "Normal eyes and visual pathways."

The spinal fluid showed no cells, protein 27 mg. per cent, sugar 67 mg. per cent, chlorides 118 meq. per liter, culture negative, colloidal gold curve 1111100000, and Wassermann negative.

An electroencephalogram taken on March 8, with chloral hydrate given for the sleeping tracing, showed low average amplitude, imperfect symmetry; alpha waves moderate amount of 8 to 11 per second activity; theta waves moderate amount of 5 to 7 per second activity in all areas; abnormal wave forms of spikes in all areas, especially on the left side. The record taken during hyperventilation was normal. The interpretation was: "Pathological pattern of a nonspecific type, with a faint lateralization to the left. These patterns are nonspecific in form but would be compatible with a seizure disorder."

Course.—After bed rest for one day in the hospital, the patient had no dizzy spells and was able to walk around. Her behavior appeared normal. She was seen by a neurologist who concluded that there was no neurological abnormality; the diagnosis was deferred.

She was discharged on March 13, 1954, after eight days in the hospital, with a tentative diagnosis of atypical or pseudo-Ménière's disease. She was directed to take Bonamine, 25 mg. t.i.d.

At home, the postural vertigo recurred almost at once. The patient also developed bilateral temporal and frontal headache, pain in the back of the neck and in the lumbosacral region. Headache later included the left posterior auricular region. On the third day after discharge from the hospital, she complained of low back pain. Headache persisted; it was chiefly localized to the forehead but occasionally involved both temples and the left mastoid region (Fig. 1). The patient was afebrile. She remained in bed at home until March 18, when she was readmitted for further study.

Fig. 1.—Distribution of referred pain (stippled zones) evoked in the patient by firm pressure on trigger areas at *X* in the clavicular (posterior) division of left sternocleidomastoid muscle. Pain appeared on left, then crossed to right forehead while pressure was sustained. Note tilt of head to place left sternocleidomastoid muscle on the slack. This position permits the examiner to encompass the muscle for demonstration of trigger areas and to lift it off underlying structures for procaine infiltration.

Second Hospital Admission.—Physical examination at this time revealed some new findings. The hypertrophied tonsils and anterior pillars of the pharynx now showed white patches of exudate.

Special examination of the skeletal muscles, which had not been done during the first hospital admission, revealed exquisite deep tenderness

bilaterally in the posterior cervical, suboccipital, and temporal muscle groups. The left sternocleidomastoid muscle was extremely tender and tense, and visibly twitched when rolled between the fingers. It felt larger and firmer than the contralateral sternocleidomastoid muscle, but contained no palpable tumor mass. Compressing the tender portion of the muscle at a point about halfway between the sternum and the mastoid process, as shown in Fig. 1, evoked vertigo, nausea, and pain in the left temple, left posterior auricular region, and across both sides of the forehead. The reference zone was discontinuous with its source. This distribution of pain matched the referred pain pattern previously mapped for trigger areas in the sternocleidomastoid muscle.[1, 2, 3, 11] When the pressure on the muscle was released, the symptoms subsided within half a minute. There was no torticollis, and motion of the neck was of average normal range without pain. Deep tenderness was present also in muscles of the shoulder-girdles, arms, and low back.

Complete neurological examination, as before, was negative except possibly for the ataxic gait. A psychogenic basis of the symptom complex was not evident.

Further exploration into the history uncovered a new etiological factor, that is, repetitive strain of the sternocleidomastoid muscles in overhead work[1]; the patient quite often climbed onto a chair and reached high over her head to pull down a ladder leading to the attic.

Laboratory Findings.—On the second admission, additional pertinent laboratory data were as follows: Throat culture showed beta hemolytic streptococci. Serum total cholesterol was 240 mg. per cent; serum total proteins, 7.2 Gm. per cent with A/G ratio 4.6/2.6; serum protein-bound iodine, 6.1 gamma per cent. The basal metabolic rate was minus 9 per cent. X-rays of the cervical spine were negative for any abnormality.

A creatine tolerance test (on a three-day creatine-creatin*ine*-free diet with a test dose of 1.32 Gm. creatine hydrate) showed 382 mg. creatine excreted on the second day of the diet (9.8 mg. per kilogram per day), 67 per cent retention of the test dose of creatine on the third day, and a creatin*ine* index of 21.1 calculated on the body weight of 39 kg. (preformed creatin*ine* output of 858 mg. and 790 mg. on the second and third days, respectively*). The total creatin*ine* output on the second day, therefore, was 1,240 mg. and the creatine thus accounts for 31 per cent of the total creatin*ine* output (normal value for children 10 to 30 per cent[12]). The normal daily excretion of endogenous creatine output on a creatine-free diet is given as 0.6 to 7.8 mg. per kilogram per day.[13]

A second electroencephalogram taken on March 26, when the patient was symptom-free after treatment, showed low average amplitude, poor symmetry; alpha waves scattered, 8 or 9 per second; theta waves low amplitude, 4 to 5 per second. Hyperventilation had no effect on the tracing. The interpretation was: "Pathological record of a nonspecific type because of abnormal amount of low frequencies. There is no evidence of an electrical focus. This record is slightly lower in amplitude than the first, and shows no lateralization which the first suggested. In this respect the second test is less abnormal than the first, but the difference is of no real consequence."

Treatment.—On the basis of the physical finding of a clinically active trigger mechanism in the left sternocleidomastoid muscle which was not associated with any specific neurological abnormality, it was concluded that this child presented the sternocleidomastoid syndrome of headache, postural vertigo, and imbalance.

On March 18, with the patient sitting comfortably in a chair, ethy

*Benedict-Folin method for determination of preformed and total urinary creatinine.

chloride spray* was applied in slow parallel sweeps over the left sternocleidomastoid muscle according to the technique described.[1, 14, 15, 16] During each sweep, the patient's head was passively rotated toward the left to place this muscle on a full stretch. The sweeps were applied in an upward direction, with an interval of two or three seconds between sweeps to allow time for evaporation of the spray and to avoid cold pain or frosting of the skin. The pain reference zones in the head were not sprayed. The immediate effect on the sternocleidomastoid muscle was a notable reduction in the deep tenderness, twitch response, and capacity of the muscle to set off referred pain to the head when the trigger mechanism was stimulated by pressure. The muscle also felt less tense. At the same time, there was noticeable improvement in the patient's balance on walking, with diminution of constant headache and of vertigo on changing position.

Spraying with ethyl chloride was repeated three times daily, and by the third day the patient walked normally. There was still some local muscle tenderness in the left sternocleidomastoid muscle, but referred pain to the head could not be elicited when pressure was applied to it as before. Minimal dizziness was evoked by a quick change of position, but there were no longer any acute paroxysms of vertigo. Daily application of the spray was continued.

The spray was also applied to the tender muscle areas elsewhere in the body with striking relief of the generalized myalgias.

Other therapy included ascorbic acid, 500 mg. twice daily, and aspirin, 0.6 Gm. every four hours during the day.

Since chronic infection is often one of the causal factors in myofascial trigger mechanisms, on March 23, adenoidectomy and tonsillectomy were performed under general anesthesia (ether with Pentothal induction).

Postoperatively the throat was very sore. However, following recovery from general anesthesia, the sternocleidomastoid muscles were relaxed and no deep tenderness, abnormal twitch response, or referred pain to the head could be elicited. Sensations of vertigo and dizziness were absent. For relief of postoperative soreness, the neck was sprayed with ethyl chloride as before. On the first postoperative day, the patient was ambulatory and was able to run and skip without dizziness or imbalance. She was discharged on the third postoperative day (March 26, 1954), free from headache and vertigo, with no demonstrable trigger areas in the sternocleidomastoid muscles. She was advised to gargle with hot saline four times a day and to continue to take aspirin, 0.3 Gm. every four hours, as needed.

She was seen six days later (April 1) because of a return of mild dizziness on sitting up quickly. She had contracted a head cold. The posterior nasopharynx was diffusely injected and edematous. Gait was normal. The posterior (clavicular) division of the left sternocleidomastoid muscle was again moderately tender to pressure and twitched on being rolled between the fingers. No referred pain was elicited to the forehead.

On April 1 procaine hydrochloride, 0.25 per cent in physiologic saline, was infiltrated into the trigger areas in the left sternocleidomastoid muscle at two sites, with the patient supine and the muscle slackened by tilting the head (left ear toward sternum). The muscle was encompassed by the fingers and lifted off the underlying structures of the neck (Fig. 1). The direction of approach with the needle to avoid major blood vessels is shown in Fig. 2. A trigger area in the clavicular part of the muscle was infiltrated first, and then one in

*The Gebauer Chemical Co., Cleveland, Ohio, supplied the ethyl chloride spray. The nozzle of the spray dispenser was calibrated to deliver a "fine" jet stream.

the sternal division. Through a single skin puncture, multiple needling with continuous injection was carried out until an abnormal twitch response was no longer elicited by movement of the needle. Hemostasis was simultaneously accomplished by stretching the skin over the muscle with the fingers of the left hand. A total of 2 c.c. of the solution was used. Ethyl chloride spray was then applied over the muscle with passive movement, as before. Immediately afterward, dizziness could no longer be elicited by change of position. There was no afterpain from the injections, although this sometimes occurs and may last a day or two. She was advised to take ascorbic acid, 200 mg. three times a day, if she felt excessively fatigued or had a cold.

Course.—The patient was presented the next day in pediatric grand rounds. She had no headache, dizziness, or imbalance. She was able to stand on one leg, stoop quickly, and remove the shoe from her other foot. Referred pain could not be set up from the previously affected sternocleidomastoid muscle, nor did it show hyperirritability on palpation.

A follow-up visit was made four weeks later (April 30), when she had been on full activity including school for three and one-half weeks. She was asymptomatic. The sternocleidomastoid muscles were not remarkable.

During the summer, she was active, participating in camp sports. She had one head cold without complications. She did not take ascorbic acid. One morning at school (Sept. 16, 1954), she stood at the blackboard reading a map. She reached up to write and felt dizzy for several seconds. The following day at school, she experienced another dizzy spell with "the room weaving," and she fainted. She was "out" for a few seconds. Afterward she was nauseated, felt sleepy, and was taken home. Her local physician found

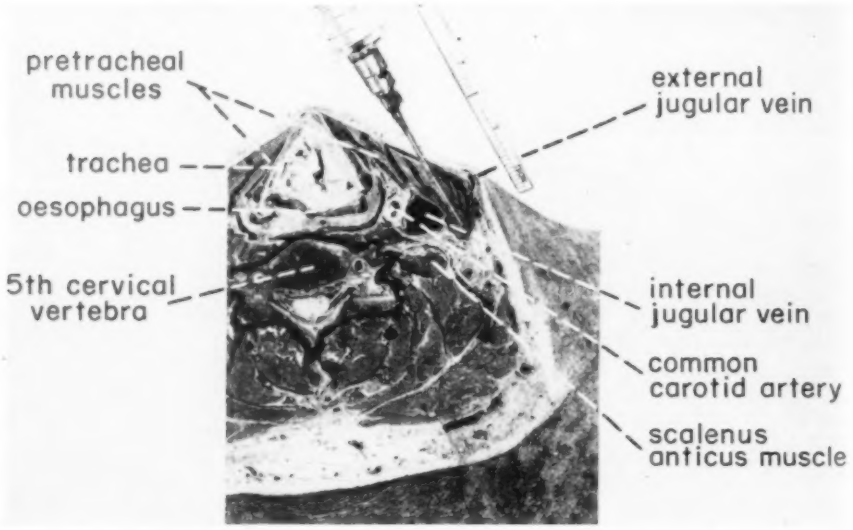

Fig. 2.—Anatomical cross-section of neck to show approach for infiltration of the sternocleidomastoid muscle to avoid large blood vessels. A 1½ inch, 24 gauge needle is shown with its tip in the posterior (clavicular) division of this muscle. The cervical vertebra is outlined in black.

that she had acute pharyngitis. He gave her Neo-Synephrine nose drops and a warm saline gargle, and she felt better. Two days later at school, she had ringing in the ears. She got up to get a drink of water and when she bent over the fountain, lowering her head almost to her knees, the ringing suddenly subsided. The following day (September 28) she was seen by us. At this time she had no complaints.

Examination on this date showed normal ocular signs, eardrums, and nasal turbinates, but the posterior wall and anterior pillars of the pharynx were injected. There was no exudate or lymphadenopathy. The clavicular division of the *right* sternocleidomastoid exhibited an increased twitch response when rolled between the fingers; the contraction was so strong as to produce a visible jerk of the head. This muscle had not been previously injected. The left sternocleidomastoid muscle was normal, and no twitch response was elicited by the same procedure. Referred pain could not be evoked by pressure on either sternocleidomastoid muscle. There was no limitation of motion of the neck.

Treatment consisted of preliminary application of ethyl chloride spray to the right sternocleidomastoid and posterior neck muscles, and then infiltration of the right sternocleidomastoid muscle with 0.6 c.c. of 0.5 per cent procaine hydrochloride in physiologic saline. The injection was made into the clavicular portion approximately at the mid-point of the muscle. Following this, ethyl chloride spray was applied. On examination immediately afterward, the abnormal twitch response was no longer present. She was advised to resume the ascorbic acid, 250 mg. twice daily, and to maintain a high mea diet, including hamburger for breakfast.

When seen three months later (Jan. 3, 1955), she reported that she had had no further episode of dizziness, headache, or imbalance. She had been taking the ascorbic acid regularly. On January 28, a third electroencephalogram was taken which showed "high average amplitude, symmetry imperfect, alpha waves small amount of 8 and 9 per second in the right hemisphere, theta waves 5 to 7 per second activity predominating in the left hemisphere and appearing to some extent in the right side also; hyperventilation normal; impression—pathological pattern, with a greater defect on the left than on the right, form of patterns not diagnostically helpful." The electroencephalograms were read by Dr. Donald J. Simons.

At the last follow-up (Feb. 10, 1955), during the ten months following infiltration of the left sternocleidomastoid muscle, the patient had had one brief recurrence of dizziness, and she had been entirely free from symptoms for over four months since infiltration of the right sternocleidomastoid muscle.

DISCUSSION

Since this report presents a syndrome new to the pediatric literature, it is pertinent to review briefly the characteristics of myofascial trigger areas.[1, 3, 11, 17, 18]

Attributes of Trigger Mechanisms.—A trigger area is a *physical sign,* in that it is discovered on physical examination. It is a localized spot of deep tenderness, with a lowered deep pain threshold. When that part of the muscle containing a trigger area is rolled under or between the fingers, a localized twitch is usually seen. A series of fasciculations may even be set off in this way. When the examiner sustains pressure on the tender spot, pain is usually evoked in a remote area. The patient points to the region where pain is felt and so delineates the reference zone.

When referred pain is not clearly elicited by pressure, contact of a needle will induce it; in this case the stimulus is probably more precisely applied. Thus, a clinically active trigger area is revealed by three things: localized deep hyperalgesia, fasciculation, and the capacity to set off referred pain.

It is not generally appreciated that *most skeletal muscle pain which constitutes a clinical problem is referred.* Body movements which involve either a full passive stretch or strong active contraction of a muscle may raise its internal tension and so mechanically stimulate the trigger area to set off referred pain.[19]

High intensity referred muscle pain may be accompanied by certain autonomic concomitant.[1, 2, 3, 17] These concomitants are localized to reference zones and include, under various conditions: lowered skin resistance, lowered skin temperature, sweating, pilomotor stimulation, vasoconstriction, or vasodilatation. Sometimes a nonpainful concomitant of the trigger mechanism, such as vertigo, is the conspicuous symptom while pain itself is negligible.

Referred pain patterns and nonpainful concomitants of myofascial trigger mechanisms are both relatively constant from person to person for a particular site of origin. Our familiarity with these attributes of the sternocleidomastoid muscle led us to the source of the disorder in the case reported. In the same way, the well-known patterns of referred visceral pain enable one to identify a viscus that is causing pain.

Clinical Features of the Sternocleidomastoid Syndrome.—The sternal and clavicular divisions of the sternocleidomastoid muscle each give rise to a specific symptom-complex.[1] Contrary to expectation, neck pain and stiffness are not features of the syndrome. Trigger mechanisms in the sternal (anterior) section are characterized mainly by unilateral pain in the forehead, orbit, cheek and throat, and occasionally in the sternum, with lacrimation, conjunctival reddening, and ptosis of the eyelid on the side of the affected muscle.

When the clavicular (posterior) division of the sternocleidomastoid muscle is involved, the symptom-complex has three components: vertigo or dizziness,* imbalance, and headache.[1] The vertigo is mainly postural.† Any of the three components may dominate, although they usually occur together. These features are illustrated by the case report. At the onset of her illness, this patient had vertigo and disequilibration without headache. About a week later, she had a period of imbalance without vertigo. Headache did not develop until two weeks after the onset of vertigo.

In some cases of postural vertigo or dizziness due to trigger mechanisms in this muscle, headache appears first.[1] The reference of pain from trigger areas in the clavicular division includes the occipital, mastoid,

*By "dizziness" we imply a vague disagreeable sensation within the head, such as giddiness, unsteadiness, or a feeling that something moves inside the cranium. "Vertigo" is a more specific sensation involving rotational movements of the subject or the environment, with marked loss of equilibrium; it may be regarded as a severe form of dizziness.

†By "postural" we mean movement of the body as a whole or the head alone which involves changes in the tension of the neck muscles, whereas "positional" involves a change in the pull of gravity on the head supported in such a way that altered tension in the neck muscles and postural reflexes are presumably not initiated.

and frontal regions on the same side, as observed in this patient (Fig. 1). As her headache increased, pain crossed to the opposite side of the forehead. A correlation of the extent of referred pain with the irritability of the trigger mechanism has been noted.[14, 19] Crossed reference of pain from myofascial trigger areas has also been described,[2, 3] and its probable pathways in the central nervous system have been investigated.[20]

Although dizziness results when trigger areas are present in only one sternocleidomastoid muscle, the sensation is not localized to one side of the head. The imbalance, however, may assume a definite pattern. In this patient the left sternocleidomastoid was predominantly affected at the onset, and she consistently veered or fell toward the right. In some other patients, however, we noted that the direction of fall was to the same side as the involved sternocleidomastoid muscle.[1]

Trigger mechanisms in the sternocleidomastoid muscles are not commonly accompanied by vomiting, although nausea is frequent. Syncope may occur, even in the absence of severe vertigo; this was the situation during the last recurrence of the symptom-complex in this patient. Impairment of hearing and tinnitus are usually absent. Neurological examination is normal, except for an ataxic gait at times. Spontaneous nystagmus is not a feature, nor is nystagmus ordinarily elicited on lateral or vertical gaze when the patient is examined during dizziness induced by change of posture.

Differential Diagnosis.—This case of postural vertigo and headache is of interest in that a battery of diagnostic tests proved negative for any disorder which originated in the head, except that the electroencephalogram showed some nonspecific variations from the normal. In particular, special tests of cerebellar, vestibular, auditory, and ocular function failed to reveal any abnormality. A Nylen test for positional nystagmus[21-23] was not performed on this patient, since the normal response after caloric stimulation, together with the normal audiograms, seemed adequate to exclude vestibular disease. The negative findings ruled out well-known causes of postural vertigo or dizziness, which include: Ménière's disease; petit mal; increased intracranial pressure; lesions of the cerebellum, brain stem, or vestibular apparatus; ocular disease; pathology of the ear; mastoiditis and sinusitis; postural hypotension and carotid sinus syndrome; hypertension; hysteria; and ingestion of toxic drugs.[1, 24]

A diagnosis of the sternocleidomastoid syndrome is not made by exclusion, however. An essential step is the demonstration of trigger areas in the sternocleidomastoid muscle. If the muscle is examined in the manner described, increased irritability in the form of an abnormal twitch response is evident, and referred pain in the regions of spontaneous headache, and transient dizziness are usually evoked. The precaution should be taken at the time of such an examination to apply ethyl chloride spray over the trigger areas. Otherwise the symptoms induced by digital stimulation may not subside and an "attack" follows.

It should be noted that torticollis, either fixed or spasmodic, is not an essential feature of trigger mechanisms in this muscle, nor does the clinical picture suggest a congenital fibrosis or "tumor" of the sternocleidomastoid muscle.[25, 26] Final proof that the symptom-complex depends on a myofascial mechanism is its prompt and prolonged disappearance with a therapeutic trial of local blocking procedures.

Therapy.—The first procedure employed in this patient was ethyl chloride spray. Symptoms were relieved during the four days in which repeated applications of the spray to the neck were made. The method of spraying is important because its mechanism of action is probably not simply that of local anesthesia but rather that of counterirritation.[3, 15, 16] Relief of pain by counterirritation is believed to be due to changes in the central excitatory state induced by an intermittent barrage of afferent stimuli,[27, 28] in this instance, the cold shock.

When symptoms recurred subsequent to tonsillectomy under general anesthesia, trigger areas in one sternocleidomastoid muscle were infiltrated with procaine. A single treatment of this kind afforded total relief of vertigo, imbalance, and headache for five and a half months. At this time, a brief recurrence of symptoms was found to depend on trigger areas in the opposite sternocleidomastoid muscle; these were similarly eliminated by one treatment.

If this were the sole instance of such a favorable response to therapy, one could not exclude the possibility that the disappearance of signs and symptoms was coincidental. When this case is viewed in the light of the larger series already reported,[1] this possibility becomes unlikely.

The technique of procaine infiltration of trigger areas[19, 29, 30] involves thorough needling of the muscle mass which contains the trigger area, with continuous injection of small amounts of the solution. If all the trigger areas have been reached, within a minute or two after the infiltration, digital pressure no longer elicits deep tenderness, a twitch response, or referred pain. It is important to check the accuracy of the injection, and if these indices have not disappeared, to reinfiltrate the muscle at a slightly different depth or angle.

Interruption of trigger mechanisms by intramuscular procaine infiltration does not depend primarily on local anesthesia by the drug, since either dry needling or infiltration with physiologic saline may eliminate the trigger areas.[19, 31] How dry needling accomplishes this is speculative. One advantage of using procaine, even in a concentration as low as 0.25 per cent, is that it lessens the intensity and duration of both local and referred pain when the needle hits the trigger area.

Etiological Factors.—If relief after local treatment of the muscle is only temporary, further search should be made, first, for additional (untreated) trigger areas and, second, for some remote disorder which provides a continuing source of noxious impulses to reactivate the myofascial trigger mechanism. As Gorrell[32] stated: "Relief of pain by local anesthetic injections does not free one from the responsibility of determining a possible serious cause for the pain."

Inciting and predisposing causes in this patient were probably:

(1) Repetitive strain of the sternocleidomastoid muscle during overhead work in pulling down the attic ladder. Either overuse or sudden injury to the muscle, as in the posteoncussion syndrome,[1] may activate a trigger mechanism.

(2) Infection in the tonsils and upper respiratory tract. After tonsillectomy, reactivation of the trigger areas with return of postural dizziness coincided with a fresh respiratory infection contracted at home.

(3) Hypometabolism. Some patients[1, 11] who are subject to recurrent attacks of skeletal muscle pain mediated by myofascial trigger mechanisms have a low basal metabolic rate, normal serum protein-bound iodine, spontaneous creatinuria, and impaired creatine retention (Benedict-Folin method). These patients do not present the classical picture of hypothyroidism. The case reported may fit this category, because of the spontaneous creatinuria (in terms of absolute creatine output for the children) and the borderline low basal metabolic rate.

Pathophysiology.—The question arises as to how a trigger mechanism in the sternocleidomastoid muscle can bring about vertigo and disequilibration. A simple explanation is that abnormal discharges from the proprioceptive receptors in this muscle, which is the chief balancing muscle of the head, misinforms the brain as to the position of the head during changes in posture. The role of tonic neck reflexes in the maintenance of equilibrium is well known.

Another hypothesis is that the barrage of impulses which reaches the central nervous system by virtue of the lowered thresholds in the trigger area results in reflex vasospasm in particular areas of the vestibular apparatus, brain stem, or cerebellum.[2, 3] These regions may be regarded as specific reference zones of the sternocleidomastoid muscle. This explanation is in harmony with Williams' statement[33] regarding pseudo-Ménière's disease, that "vasospasm of the internal auditory artery, an end-artery which supplies the crista of the horizontal semicircular canal, could readily account for recurrent attacks of vertigo without signs of cochlear (auditory) disturbance." Rambo and associates[34] found in the monkey that neither sympathetic nor parasympathetic denervation of the inner ear produced signs of damage to the cochlea or labyrinth during ten days to two months. Furthermore, no significant immediate change in the caliber of the labyrinthine vessels was observed. These ablation experiments, however, do not reproduce conditions of prolonged stimulation. In the sternocleidomastoid syndrome, it is still possible that both disturbed proprioception and localized reflex vasospasm in the brain operate together to produce the symptom complex.

One wonders how many of the cases of postural vertigo or dizziness without auditory phenomena, which like this one were termed pseudo-Ménière's disease, may represent syndromes of the sternocleidomastoid muscles. The number of unclassified cases of this type is quite large. Lindsay[35] states,

"In general medical practice, attacks of vertigo occur more frequently without any associated auditory disturbances and without any definite disease of the central nervous system. Vertigo of this type frequently cannot be localized definitely to either the central or the peripheral vestibular apparatus. The general term 'pseudo-Ménière's syndrome' has been frequently applied to this type of attack of vertigo."

SUMMARY

In an 11-year-old girl, attacks of postural vertigo and headache were traced to their source in trigger areas in the sternocleidomastoid muscle, the chief balancing muscle of the head. This is the first case of this syndrome to be reported in the pediatric literature.

Etiological factors, diagnosis, treatment by local measures directed at interrupting the trigger mechanism, and the pathophysiology of the sternocleidomastoid syndrome are discussed.

A concept of the myofascial trigger area as a physical sign with predictable patterns of referred pain and reflex autonomic concomitants is presented.

Every patient with headache, postural vertigo or dizziness, and imbalance should be examined routinely for related trigger areas in the sternocleidomastoid muscles. A therapeutic trial with ethyl chloride spray and procaine infiltration of the trigger areas should be made. Temporary or partial relief implies either insufficient treatment or reactivation of the trigger mechanism reflexly by remote disease.

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Philadelphia Sept. 14, 1785. Sickness is at this time very prevalent in most parts of the country, and many grown persons but chiefly children, have been carried off. We are told in particular of one precinct in Ulster County, where almost every child under the age of six years, have been snatched from the tender embrace of their affectionate parents by that grim and inexorable tyrant DEATH.

NEW HAMPSHIRE GAZETTE AND GENERAL ADVERTISER.

THE EFFECTIVENESS OF CHLORPROMAZINE (THORAZINE) WITH CEREBRAL PALSIED CHILDREN

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THE current efforts at developing over-all treatment programs for cerebral palsied children utilize all available techniques and procedures in medical and allied fields. Not only do present methods need evaluation to determine their effectiveness, but new advances in treatment need evaluation to determine their worth for inclusion in the therapeutic programs.

The use of drug therapy as an adjunct in cerebral palsy treatment has been accepted for some time. However, studies of previous new drugs have either been negative[1] or inconclusive.[2] In these evaluation studies, it has been recognized of utmost importance to test the drug against the effect of a placebo. A new drug can be considered to be of value only if its results are significantly better than those obtained when the child is receiving a placebo.

Chlorpromazine (10-[3-dimethylaminopropyl] - 2 - chlorphenothiazine hydrochloride) has been described as a central nervous system depressant.[3] Preliminary tests have indicated that chlorpromazine acts at the cortical and subcortical levels in the cerebrum, at the diencephalon in the medulla, and, to a lesser extent, on ganglia and the peripheral autonomic system. Its relaxant effect is thought to be the result of interruption of neural impulses passing between the diencephalon and the cerebral cortex. Tests in animals and human beings indicate that chlorpromazine is relatively nontoxic, and has a fairly wide range of application to control of nausea and vomiting, intractable pain, hiccoughs, as well as anxiety states and a variety of mental and emotional disturbances.

The requirements for a successful drug in cerebral palsy should be: (1) beneficial effect on the child's overall behavior, (2) relaxant effect on musculature, (3) palatibility and ease of administration, (4) low toxicity. This study will evaluate chlorpromazine with these criteria in mind.

METHODS

Subjects.—The subjects were eighteen cerebral palsied children, aged 1 to 12 years (modal age 3 years), who had been attending the Meeting Street School for at least eight months prior to the beginning of the study, either in the preschool group or regularly on an appointment basis. All children had been well followed medically, and had been given an individual psychological examination. There was a wide range of physical handicap, from mild (six) through moderate (two) to severe (ten). A mildly handicapped child is one whose gait, speech, and physical activity appear

From the Crippled Children & Adults of Rhode Island, Inc., the Meeting Street School.

normal except that fine precision of movement may be impaired. A moderately handicapped child is able to walk unassisted, although his gait may differ from the normal. Generally, he has only fair use of one upper extremity. His speech is understandable, but may be indistinct. A severely handicapped child is usually unable to care for all his own bodily needs because he is unable to walk unassisted, talk clearly, or has little use of his hands. There was a wide range of intelligence included, from average (three) through borderline (four) to mentally defective (eleven).

Because chlorpromazine was being evaluated for its beneficial effects on behavior as well as its relaxant effect on musculature, the children were classified behaviorally as follows: (1) there were four children who had "body anxiety," that is, children who showed fearful reaction to their body position in space (for example, extreme fear of falling, fear of heights, etc.), (2) there were four who were classified as "anxious" due to emotional or environmental causes, rather than the above "organic anxiety," (3) the remaining ten cases were classified as "not anxious."

Experimental Design.—Each subject was his own control. That is, the group was divided in half at random, with one half (Group A) receiving the drug first for a two-week interval and then the placebo for a similar period. The other half (Group B) received the placebo first, then the drug. One of us (R. H. H.) alone knew when the child was receiving medication or a placebo.

Drug Dosage.—Chlorpromazine (Thorazine) was administered as an orange-flavored syrup. One 5 c.c. teaspoonful contained 10 mg. of chlorpromazine hydrochloride. The placebo, prepared by the manufacturer especially for this study, was identical in taste, odor, and color with the syrup. The dosage calculated for children up to the age of 5 years was 10 mg. three times a day. For older children, the dosage used was 20 mg. three times a day.

Rating Procedures.—Several rating procedures were utilized.

1. Physical and occupational therapists rated each child's reactions in at least two of four experimental situations:

(a) Plank walking. Child is asked to walk 4 feet on a 1-foot-wide board placed 3 feet above floor level. Performance ability and behavior were recorded.

(b) Blanket pulling. A young child, unable to walk, was placed in a blanket on a table in a supine position, and the blanket was pulled quickly under the child. Child's behavior was recorded.

(c) Blindfold situation. Child played "pin the tail on the donkey" with the therapist. The child's reactions to being blindfolded were recorded.

(d) Ring suspension. Child reaches for gymnasium rings, 5 feet above the floor level, while standing on a chair. While suspended by his arms, the chair is removed from under the child. His ability to grasp and hang onto the rings and his behavior were recorded.

Each child was tested individually and rated for physical performance and behavior by physical and occupational therapists independently. Observation records were kept to note the child's improvement or nonimprovement in physical performance. A five-point rating scale that indicated degrees of anxious behavior was also

utilized. The total anxiety score was made up of combined test ratings in the experimental situations. The ratings were taken (1) before any drug or placebo was administered, (2) while on the drug, and (3) while on the placebo.

2. The speech therapist and nursery school teacher rated each child attending the preschool group on his cooperation and participation in group play. The amount of greater participation in play was taken to be indicative of either greater relaxation or lessened withdrawal.

3. Physical and occupational therapists were asked to make predictions when Group A was on the drug and when Group B was on the drug, as to which children were receiving drug and which were not.*

Laboratory Tests.—Laboratory tests included complete blood counts, complete urinalysis, clot retraction time, and blood platelet counts. Liver function tests included urine urobilinogen, icterus indices, thymol turbidity, and cephalin flocculation tests. These were done six months after initial study had been completed. Thirteen of the children studied were still on the drug at the time of the laboratory analysis.

*The null hypothesis was tested by X^2 corrected for continuity. Clinically, if there is no effect of the drug, therapists are expected to discriminate between children on or off the drug no greater than chance.

RESULTS

1. *Experimental Situations.*—Therapist rating scales indicated that nine (50 per cent) of the eighteen children studied showed improved behavior on medication, as compared to three (17 per cent) who improved while on placebo. This difference is statistically significant at the .01 level. The improvements appeared mainly in behavioral adjustment to the experimental situations, rather than any relaxant effect on musculature. (Table I.)

2. *Lessened Body Anxiety.*—Of the four children classified as having "body anxiety," four, or 100 per cent, were rated as improved. On the other hand, there was improvement in only one of four of the children who were anxious because of environmental stress alone. (Table II.)

TABLE I. CLASSIFICATION OF CHILDREN SHOWING IMPROVEMENT WHILE RECEIVING CHLORPROMAZINE

CASE	DIAGNOSIS	DEGREE	I. Q.	AGE (YR.-MO.)
1	Spastic quadriplegia	Severe	40	7-6
2	Spastic paraplegia	Moderate	40	3-8
3	Spastic diplegia	Moderate	25	2-11
4	Spastic right hemiplegia	Moderate	38	3-2
5	Spastic left hemiplegia	Severe	27	1-2
6	Cerebral palsy, mixed	Severe	100	12-1
7	Cerebral palsy, mixed	Moderate	104	3-5
8	Spastic diplegia	Severe	14	5-9
9	Spastic quadriplegia	Severe	14	3-1

TABLE II. ORIGINAL RATINGS AND BEHAVIORAL IMPROVEMENT ON CHLORPROMAZINE

	BODY ANXIETY	ENVIRONMENTAL ANXIETY	MENTAL DEFICIENCY (NONANXIOUS)
Total	4	4	10
Improvement	4 (100%)	1 (25%)	4 (40%)

Four of the ten children rated as "nonanxious" improved by being more relaxed behaviorally. They were happier, less irritable, readier to adjust to new situations. Parents reported these children ate and slept better, and were less constipated.

3. *Therapist Predictions.*—Both therapists who were asked to predict which children were on the drug, predicted correctly in fifteen of eighteen children. This prediction is significantly greater than chance at the .01 level.

4. *Correlation of Therapists and Doctor's Ratings.*—Doctor's ratings of improvement or nonimprovement were correlated with therapists' ratings of improvement or nonimprovement. There was agreement on fourteen of eighteen children. This agreement is significant at the .01 level of confidence.

5. *Administration.*—There was no difficulty in getting parents to administer the drug in the liquid form. Apparently, the children found it palatable, and without any prolonged adverse effects. During the first few days of drug administration, some children were listless and slept longer than usual. Dizziness and nasal congestion were not reported, while constipation was reported in one case.

6. *Parents' Reports.*—Of seventeen parents who reported, eight reported improvement, five no change, and four reported the child was worse on the drug. Improvement was reported as increased appetite, sleeping better, less irritable, more relaxed. Children reported as worse were said to be more irritable. There was agreement in only seven out of seventeen cases between therapist and parents' reports, even though the parents reported improvement in eight children (similar to the total number rated as improved by the school staff), i.e., as many parents reported improvement as the therapists, but these were different children. Apparently, parents look for different criteria of improvement than do professional workers.

7. *Drug Toxicity.*—In seventeen of the eighteen cases, there was no evidence of any toxicity referable to the blood, urine, or liver. In one case, a 3 plus cephalin flocculation test was positive without any other corroborative evidence of liver damage. This was noted six months after the child had discontinued medication.

DISCUSSION

In the light of the requirements presented for a successful drug in cerebral palsy, chlorpromazine was found to have (1) beneficial effect on the child's over-all behavior, (2) palatibility and ease of administration, and (3) low toxicity.

There was no appreciable specific beneficial or deterrant effect on muscle status when the child was examined by the usual clinical methods. However, the child's good humor made it easier for therapists to do therapy with a more relaxed child. The results of this study emphasize that looking for specific improvement in muscle status (i.e., diminution of spasticity) is not as important as the over-all behavioral improvement a child may make.

To further supplement the month's experimental study, seventeen of the eighteen children continued to receive medication from one to ten months (mean: 4.3 months) after completion of the study. Eleven of these children continued to improve in physical and emotional adjustment.

Most remarkable was the dramatic improvement in four children while on the drug. One boy, a 12-year-old, severely handicapped, mixed athetoid-spastic quadriplegia who had never walked before in his life, gained enough confidence to try to walk without help. Another child, a 3-year-old, severely handicapped, spastic quadriplegia, who had cried continuously, and laying in seissors position on the doctor's examining table, sat by herself unsupported on the edge of the table, and spoke several words clearly. Unfortunately, there was some regression physically and behaviorally when the drug was discontinued.*

Analogous to the pain-relieving effects of chlorpromazine, in cerebral palsied children the physical handicap is still there but the child is not as much aware of it as previously.

This study has emphasized that generally too little attention is paid to the psychological factors in cerebral palsy, particularly anxiety and self-awareness associated with the child's physical disequilibrium in space. It is felt that this drug may open up new research possibilities in the area of psychobiological research in cerebral palsy. In this way, a greater understanding of the integration of the psychological and physiological aspects of behavior may eventually be used to enhance the therapeutic armamentarium.

*From a psychological point of view, it was interesting to note certain relationships between body anxiety, physical handicap, and mental level. From the present information available, the following tentative conclusions can be drawn. Body anxiety, as we have defined it, may or may not be typical of a severely physically handicapped child, but body anxiety does not appear to occur in mildly physically handicapped children. Body anxiety does not occur in low-grade or middle-grade mentally deficient children regardless of the degree of physical handicap. It would thus appear that there must be a certain degree of intelligent self-awareness in the child for body anxiety to be experienced.

SUMMARY AND CONCLUSIONS

Chlorpromazine was evaluated for its physical and behavioral effects on eighteen cerebral palsied children. Improvement was found in 50 per cent of the children, a significantly greater improvement than when the children were merely receiving a placebo. Of four children rated as having "body anxiety," all (100 per cent) showed improvement. Both intelligent and mentally deficient children showed increased relaxation and lessened anxiety, were happier, less irritable, and easier to manage. There were no toxic effects noted, clinically or by laboratory studies.

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CEREBRAL PALSY

A Practical Routine for Discerning Oculomotor Defects in Cerebral Palsied Children

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CARLSON[1, 2] and Miller[9] found eye defects existing in over 50 per cent of the patients with cerebral palsy resulting from central nervous system derangements. Guibor[6, 7] found 75 per cent of a series of 142 cerebral palsied children possessed ocular defects. These defects often exist at birth. They are not usually noticed for a period of from one to three years. They are rarely treated adequately so as to develop good vision and adequate motor ability of the eyes. Freud[5] recognized the association of ocular symptoms in the cerebral palsied children, but did not discuss their adequate treatment. Such defects are those of the motor system —crossed eyes, conjugate deviations (both eyes deviating to one side or upward), and/or nystagmus (a to-and-fro movement). With these defects there exists a visual loss (amblyopia) which cannot always be overcome by treatment. Such anomalies of the eyes result in a loss of binocular coordination and depth perception. Therefore, certain of these paretic children fail to develop hand and eye coordination, walking, talking, and reading as well as if normal ocular conditions existed.

In addition, a prolonged turning of an eye toward the nose permits the inner ocular muscles to shorten and the outer muscles to lengthen. The face on the side of the deviating eye fails to develop, and there exists an atrophy of the tissues.

Foerster[3, 4] stressed the fact that infantile hemiplegia is associated with lesions in the cortex which are different than those found in adult hemiplegia. Kennard and Ectors[8] have proved that recovery from experimental cortical lesions in the young is much greater than in the adult. The ability to recover from ocular defects is, likewise, greater in the infant.

Where defective motor coordination exists, certain abnormal reflexes result which may be associated with the spread of impulses displayed especially by patients with athetosis. When the child with athetosis recovers from his ocular motor and visual disturbances as a result of treatment, his athetosis decreases. When his glasses are removed, his athetosis recurs. Children with ataxia may be affected similarly. Phelps[10] mentioned the fact that in ataxia, the

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disturbed balance makes it necessary for the child to learn to orient himself by means of sight and other sensations. He discussed the use of braces. I believe in proper cases that lenses, prisms, and atropine cycloplegia also aid in correcting and overcoming abnormal eye movements, and, therefore, help these patients in coordinating eye motor activity, at times in walking, and in the use of their hands.

Those who see patients with cerebral palsy should be interested in the eyes as well as in the generalized motor and sensory abnormalities existing in these children.

Phelps,[10] in his discussion of rigidity associated with petechial hemorrhages from anoxemia, estimated the percentage of cerebral palsied persons, and believed that for every 100,000 population there are seven with cerebral palsy. Of these, 56,000 are under 20 years of age. From recent statistics concerning ocular defects in cerebral palsy, there are at least 42,000 with strabismus or other ocular defects. *Should we not consider such ocular disturbances in these patients in our training program?*

The purpose of this paper, therefore, is to present a few simple tests which will aid the examiner to ascertain the presence of an ocular motor defect or of a subnormal vision. When ocular defects are found and diagnosed by the specialist in cerebral palsy, he can then refer the patient to an eye doctor who is interested in children's eye diseases and their associated motor anomalies.

The tests to determine the presence of an ocular motor defect consist of the corneal reflection and the rotation tests.

The corneal reflection test is used to determine the presence of a strabismus or crossed eye. This test requires ten seconds and a close observation of the child's eyes, so that many pediatricians and ophthalmologists utilize the corneal reflection test to examine small children and infants. The corneal reflection test consists of shining a flashlight as the infant gazes at the light. The examiner, meanwhile, notes the position of the light reflection from the surface of each cornea. A tiny babe of 2 or 3 weeks of age will watch the light and often follow it with his eyes as the doctor moves it from side to side.

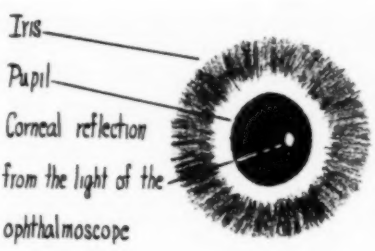

Fig. 1.—Normal position of spot of light reflected from the cornea of the right eye. Note that the reflection from the corneal surface of the right eye is toward the nasal portion of the right pupil.

TECHNIQUE OF CORNEAL REFLECTION TEST TO DETERMINE THE PRESENCE OR ABSENCE OF A STRABISMUS (PHYSIOLOGICO-ANATOMIC BASIS)

By observing Fig. 1, we see a diagrammatic illustration of the light reflection from the right cornea. A flashlight is held in the hand of the observer while the patient gazes at the light with his right eye (the left eye being covered). Note that the reflection is toward the nose (Fig. 1), and not in the central pupillary portion. This is the position of the light

for the normal eye. The infant's left eye, likewise, displays a normal reflection of the light from his left eye when the right eye is covered (Fig. 2).

Binocular Corneal Reflection Test for Esotropia.—Suppose the right eye of any one infant deviates toward the nose—the reflection of the light from the right cornea will not remain decentered nasally, but will be toward the lateral side (Fig. 3.)

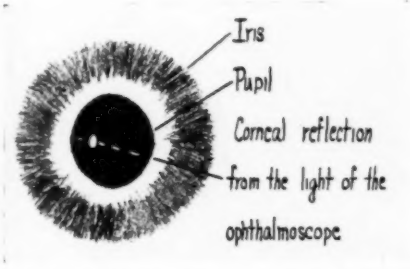

Fig. 2.—Normal position of spot of light reflected from the cornea of the left eye. Note that the reflection from the corneal surface of the left eye is toward the nasal portion of the left pupil.

Technique: Both eyes of the infant, remaining unoccluded, gaze at the light held by the examiner. The light will now appear lateral to the normally reflected position if a right strabismus is present. Thus, the examiner may conclude that the child has a right esotropia of 10, 20, or 45 degrees, depending upon the position from which the light is reflected from the patient's right cornea.

In a similar way, the left eye may be deviating toward the nose. In this instance, both of the infant's eyes remain unoccluded as it gazes at the flashlight held by the examiner 2 or 3 feet from his face. The corneal reflection will then be lateral to the normal nasal position.

It must be known that early diagnosis of a crossed eye by the corneal reflection test and early treatment to compel the crossed eye to focus or to fix can be secured by dropping atropine once each week into the straight eye. The straight eye will be blurred

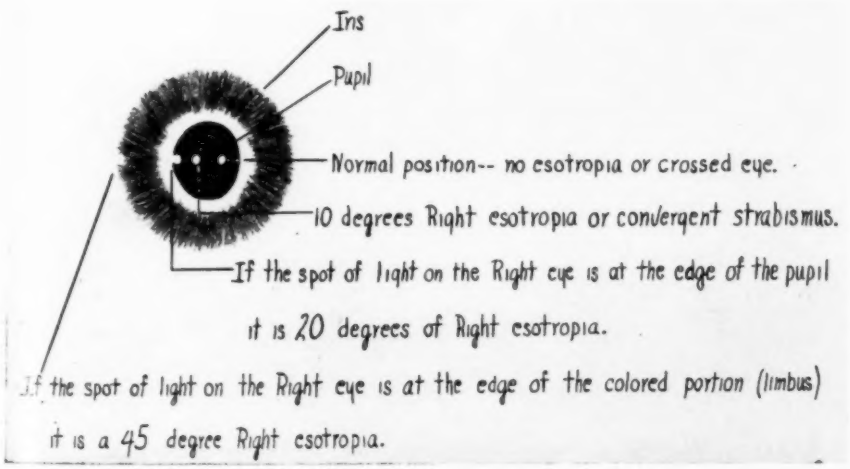
Iris
Pupil
Normal position-- no esotropia or crossed eye.
10 degrees Right esotropia or convergent strabismus.
If the spot of light on the Right eye is at the edge of the pupil
it is 20 degrees of Right esotropia.
If the spot of light on the Right eye is at the edge of the colored portion (limbus)
it is a 45 degree Right esotropia.

Fig. 3.—Composite diagrammatic view of the reflections of light from the cornea of the right eye to demonstrate concisely the possible positions of reflections.

Fig. 4.—Hypertonic athetoid type of cerebral palsy with insufficiency of levoversion. *A*, Hyperextension of upper extremities in attempted gaze to left. *B*, Gaze to right normal. *C*, Spasmodic supraversion and dextroversion in attempted gaze to left. *D*, Head movement in gaze to left and extension of head instead of rotation of eyes. *E*, Fixing with left eye, showing right eye turning in.

for two days by the drops each week. The crossed eye will be compelled to focus at least two days each week, and it will, therefore, develop vision after a long period of time with blurring of the better eye. The parents of the patient must be advised that the straight eye will turn, which is an indication that the crossed eye is focussing. The turning of the better eye is a good sign, and need not alarm the doctor or the parents.

TECHNIQUE OF EXAMINATION TO DETERMINE A CONJUGATE WEAKNESS (ROTATION TEST)

The examiner watches the movements of the patient's eyes as the child gazes at a light as it is moved slowly from side to side, up or down. Youngsters under 6 months of age can gaze up and down easily, but usually not laterally. With much effort, however, he may look from side to side without moving his head. Normally, a child 6 months or older can follow the light with both eyes and can hold a lateral position for three seconds.

If the two eyes cannot move to the right or left, or up or down, or if the lateral position of gaze cannot be maintained, a conjugate defect is present. Conjugate defects are disturbances in ocular movements and involve both eyes. They are paretic or spasmodic in character. The rotation tests should be repeated several times before a definite decision can be reached concerning conjugate defects.

Fig. 4 demonstrates such a patient with bilateral spastic hemiparesis. She displays a head-turning to the left to compensate for an insufficiency of gaze to her left (levoversion). Hypertonus of the right hand is extreme, *A*; she can gaze to the right, *B*, without excessive effort and maintain this position (dextroversion) for a few seconds. In attempting to gaze to the left her eyes turn spasmodically to the right and she is unable to move her eyes toward the left. Note the severe spasms of her facial muscles in *C* as she attempts to move her eyes to the left. Instead of moving her eyes, she must move her head to compensate for the insufficiency of levoversion (gaze paralysis to the left), *D*. When gazing straight ahead she resumes the position of her head and eyes as seen in *A*. These photographs are presented in order to clarify the appearance of the insufficiency of gaze to the left.

Of the 142 patients with cerebral palsy studied in a previous report, there were forty-seven patients with such conjugate weaknesses (33 per cent).

TECHNIQUE TO DETERMINE DISTANT VISUAL EFFICIENCY

The testing for distant visual acuity usually requires that letters be presented from a distance of 20 feet; the chart (Fig. 5) requires that the "E" symbol be shown to the child from a distance of 10 feet only. This "E" chart at 10 feet can be employed for children 3½ years or older.

Technique: The child is seated comfortably and told he can play the "E" game. His left eye is occluded—the examiner standing *10 feet* away holds the "E" symbol chart and asks the patient to point in the direction to which the "three fingers" point. The examiner points first to the largest "E" which is easily seen by the average child.

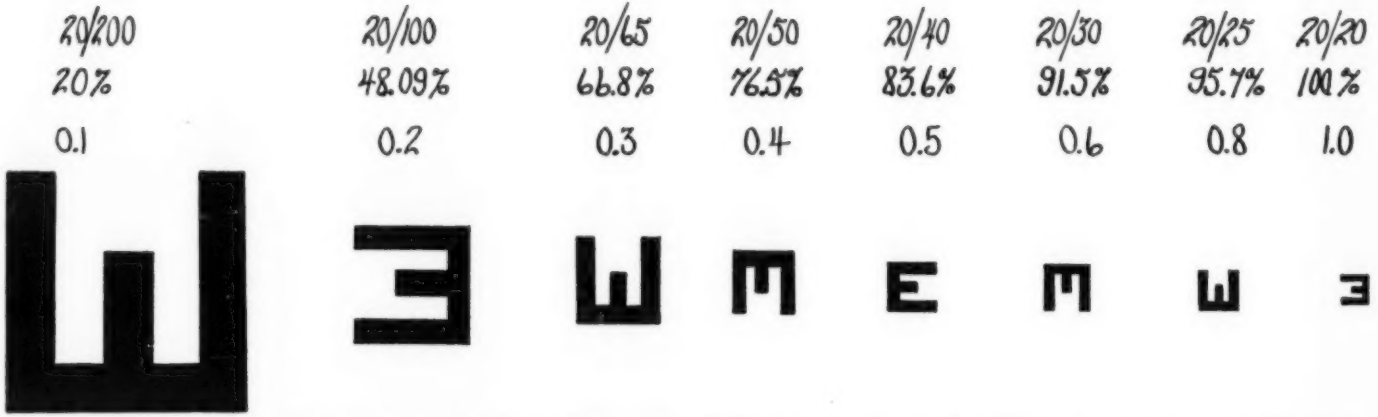

Fig. 5.—Chart for determining visual efficiency at 10 feet. The examiner should stand 10 feet from the patient with a 60 watt light on the chart. The patient should cover the left eye and point in the same direction to which the "E" points. Visual acuity and visual efficiency may be determined by the method. After visual acuity is determined in the right eye, the right eye should be occluded and visual acuity in the left eye determined. Visual determination by this method is impossible before the age of 3½ years. (Note: These notations are for a distance of 20 feet; chart is used at a distance of 10 feet.) (Chart reduced ⅙.)

If the examiner must approach closer to the patient than 10 feet to permit the child to see the large "E" accurately, the visual acuity is less than normal. Suppose the doctor holding the chart approaches to within 3 feet of the patient and the child sees only the large "E," his visual acuity is 3/200, or 3 per cent.

Each eye is tested separately. After the vision of the right eye is obtained, the patient's right eye is occluded and the vision of the left eye determined similarly.

SUMMARY

Ocular defects exist in over 50 per cent of patients with cerebral palsy resulting from central nervous system derangement.

These ocular motor defects should be detected before degeneration of vision occurs in these children. Early treatment of these motor defects will develop vision and may improve general motor ability, especially in patients with athetosis or ataxia.

Simple tests are, therefore, suggested for detecting the presence of strabismus by the corneal reflection test, conjugate defects by the motility test, and subnormal vision by the means of the "E" game. An "E" chart for 10 feet distance testing instead of 20 feet distance is presented. This "E" chart gives percentages of visual efficiency as well as ordinary visual notations.

Other tests such as the near vision and fixation tests are purposely omitted in this paper.

It is a pleasure to thank Drs. Richard Gamble and John Bigler for their help in the preparation of this paper.

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NUCLEASES IN THE CEREBROSPINAL FLUID

IV. Dephosphorylation of Nucleic Acids by the CSF, Especially of Poliomyelitis Patients

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THE first phase of enzymic hydrolysis of nucleic acids (NA), depolymerization by nucleases[19, 20, 21, 23] in the cerebrospinal fluid has been described.[14, 15] A characteristic pattern was observed in poliomyelitis specimens.[18] These findings stimulated us to study further steps in the NA metabolism, which ultimately lead to the complete disintegration of the complex molecule. The present report deals with liberation of inorganic phosphate from pentose and desoxypentose nucleic acids (PNA and DNA) and their derivatives by CSF enzymes. The ferment systems involved are nucleophosphatases,[11] or nonspecific diesterases,[9, 30, 31] called by one writer oligonucleotidases,[24] which produce mononucleotides from depolymerized NA. Dephosphorylation of the nucleotides is brought about by nucleotidases,[25] which are monoesterases and, in all probability, identical with acid and alkaline phosphatases.[6] There is some evidence, however, supporting the existence of enzyme systems hydrolyzing exclusively the 3-P bonds of nucleotides.[22] The specificity is already proved for 5-nucleotidases, hydrolyzing muscle adenylic and inosinic acids[27]; therefore the presence of these enzymes in the CSF will be reported in detail separately.

From the Department of Hygiene and Preventive Medicine, University of Toronto. This work was financed by a Mental Hygiene Grant.

METHODS

The method is based on the assumption that the source of inorganic phosphate (IP), under the conditions of these assays, is the NA, and its increase is due to the activity of various enzyme systems present in the CSF.

Highly polymerized PNA and DNA were used as substrates in 0.1 per cent concentration; the former dissolved in borate, acetate,[13] or in Veronal-acetate[26] buffer of pH 5 to 7.6±; the latter in Veronal-acetate buffer, pH 7±.

Spinal fluid, 0.1 to 1 ml., and 5 ml. of NA solution were mixed. Magnesium sulfate was added in 0.003 M final concentration and the volume brought up to 10 ml. with buffer. Substrate and buffer with 0.1 to 1 ml. physiological saline and CSF in buffer alone were run in parallel, as controls. One drop of chloroform in each tube served as preservative. After incubation, the IP concentration was determined by the method of Fiske and Subbarow.[5] For this purpose, undegraded nucleate and proteins were removed by the McFadyen reagent[14] in the PNA series, and by chilled 20 per cent trichloroacetic acid in the DNA series.[9] In other aliquots of the filtrates total acid soluble phosphorus (TASP) was determined by King's method.[10, 14] Values of the controls were deducted from those of the systems and the differences

expressed as microgram per 10 ml. of the system, was the measure of the enzyme activity.

For the detection of oligonucleotidases two alternative approaches were tried. Nuclease-predigested PNA and DNA were used as substrate in the first method and increase of IP and TASP micrograms per milliliter as determined in a modified McFadyen filtrate.[9] The second technique consisted of the use of pure magnesium-

techniques of Shinowara and associates.[29] Composition of the systems and controls was similar to those of the NA assays in all these investigations. The difference between the IP value of the system and controls indicated the degree of enzyme activity. All the determinations were made in duplicate. Samples were kept frozen at -25° C., thawed and centrifuged at room temperature before use. Sterile routine was strictly observed in the handling of ingredients.

TABLE I. DEPHOSPHORYLATION OF PNA BY CSF

GROUP	TOTAL NUMBER OF SAMPLES	NUMBER WITH ACTIVITY	RANGE OF INORGANIC PHOSPHATE INCREASE IN μG/10 ML.	MEAN ± STANDARD ERROR
1. Normal and neurologically normal	36	17	0 to 3	0.7 ± .002
2. Meningitis	50	38	0 to 22	16 ± .05
3. a. Poliomyelitis	100	94	0 to 18	15 ± .02
b. Other virus diseases	20	17	0 to 16	—
4. Syphilis	50	32	0 to 9	6 ± .04
5. Miscellaneous neurological conditions and psychoses	50	23	0 to 20	5 ± .05

PNA—0.1 percent in buffer pH 6.8±, 0.2 ml. CSF, 0.003 M $MgSO_4$, buffer up to 10 ml. volume, 1 drop of chloroform. Incubation 16 hours at 37° C.

oligonucleotides of DNA,* as described by Hurst and associates.[9] Russel's viper venom† served as standard diesterase material.

For the assays of 3-nucleotidases, PNA gently hydrolyzed by dilute Na_2CO_3, and single mononucleotides‡ or an equimolar mixture of four, simulating tetranucleotides, were used as substrate in 0.1 per cent solutions in water. Desoxycytidylic acid§ was the only one of the nucleotides of DNA examined during this work. Acid and alkaline phosphatases were measured on glycerophosphate substrate by the

*Courtesy Dr. G. C. Butler, Department of Biochemistry, University of Toronto.

†Supplied by Haffkine Institute, Bombay.

‡Supplied by Nutritional Biochemicals Corporation, Cleveland, Ohio.

§Courtesy Dr. G. C. Butler, Department of Biochemistry, University of Toronto.

RESULTS

The 360 individuals CSF's examined were derived from five clinical groups: (1) normal and neurologically normal, (2) meningitides, (3) poliomyelitis and miscellaneous virus diseases, (4) syphilis, (5) neurological and psychotic conditions. Criteria of classification were outlined previously.[16, 17, 18] Table I presents the results obtained with PNA substrate.

Normal and neurologically normal CSF exhibited slight increase of IP after incubation. Some of the meningitis and nearly all of the polio specimens showed the most intense activity of all the clinical groups examined. The majority of CSF's from neurological and psychotic cases did not ex-

hibit any change but, as an exception, high values were encountered in a few instances. The highest percentage (94 per cent) of positive assays in polio specimens is noteworthy. This is significant, because this was the largest clinical group and the low standard error indicates good homogeneity in the distribution of the IP values.

Table II illustrates the results with DNA substrate.

Of the normal and neurologically normal samples, only eleven out of thirty-six displayed some activity; the majority of these were from non-neurological diseases. The highest activity, twenty-eight out of fifty, was observed in syphilis followed in order by the miscellaneous virus samples, meningitis, and polio groups. The amount of IP was generally lower than in the PNA assays.

Using examples taken from the highest values observed, Tables III and IV illustrate the presence of various enzyme systems which are responsible

TABLE II. DEPHOSPHORYLATION OF DNA BY CSF

GROUP	TOTAL NUMBER OF SAMPLES	NUMBER WITH ACTIVITY	RANGE OF INORGANIC PHOSPHATE INCREASE IN μG/10 ML.	MEAN ± STANDARD ERROR
1. Normal and neurologically normal	36	11	0 to 4	0.3 ± .01
2. Meningitis	50	24	0 to 5	3 ± .03
3. a. Poliomyelitis	100	48	0 to 8	3 ± .02
b. Other virus diseases	20	13	0 to 7	—
4. Syphilis	50	28	0 to 10	5 ± .03
5. Miscellaneous neurological conditions and psychoses	50	22	0 to 8	4 ± .04

DNA—0.1 percent in buffer pH 7.0±, 0.2 ml. CSF, 0.003 M $MgSO_4$, buffer up to 10 ml. volume, 1 drop of chloroform. Incubation 16 hours at 37° C.

TABLE III. DEPHOSPHORYLATION OF NA AND OF OLIGONUCLEOTIDES (EXAMPLES)

DIAGNOSIS	SUBSTRATE	pH	INCREASE IN μG/10 ML. IN IP	INCREASE IN μG/10 ML. IN TASP
Nonparalytic poliomyelitis	PNA	6.5	25	129
H. influenzae meningitis	DNA	7.0	13	75
Paralytic poliomyelitis	Nuclease predigested PNA	5.5	16	63
E. coli meningitis	Nuclease predigested DNA	8.48	18	48
Neurosyphilis (treated)	Desoxy-oligonucleotides	8.48	5	16
Brain atrophy	Desoxy-oligonucleotides	8.48	3	10

4 ml. substrate, 0.1 to 0.01 percent in buffer, 0.2 to 1 ml. CSF, 0.003 M $MgSO_4$, buffer up to 10 ml. volume, 1 drop of chloroform. Incubation 16 hours at 37° C.

TABLE IV. DEPHOSPHORYLATION OF MONONUCLEOTIDES (EXAMPLES)

DIAGNOSIS	SUBSTRATE	pH	INCREASE IN IP μG/10 ML.
Neurosyphilis (treated)	Alkali hydrolysed PNA	9	8
Subdural hemorrhage	Mixture of 4 pentose-nucleotides (A:G:C:U acid)	9	18
Neurologically normal	3-adenylic acid	9	0
Meningococcal meningitis	3-guanylic acid	9	28
Bulbar polio	3-cytidylic acid	9	18
Brain tumor	3-uridylic acid	9	3
Alcoholic encephalopathy	desoxy-cytidylic acid	9	5

2 to 4 ml. substrate, 0.1 percent in distilled water, 0.2 to 1 ml. CSF, 0.003 M $MgSO_4$, buffer up to 10 ml. volume, one drop of chloroform. Incubation 16 hours at 37° C.

for the dephosphorylation of NA and nucleotides. Simultaneous changes in the two phosphorus fractions indicated the simultaneous activity of nucleases and nucleotidases.

This relationship was further evidenced by experiments using NA predigested by nuclease as substrate. Pure desoxyribo-oligonucleotides were also readily hydrolyzed by the CSF, resulting in a simultaneous increase both of the IP and the TASP due to concomitant action of diesterases and monoesterases. Russel's viper venom served as a check for the splitting of oligonucleotides; there was good agreement between the mode of action of this concentrated enzyme and the CSF's, except for the quantitative difference in favor of the venom.[9]

Table IV illustrates a further step, with more degraded substrates.

The majority of polio, meningitis, and syphilis samples caused increase in IP when incubated with PNA previously hydrolyzed by alkali. A similar picture was produced in individual pentose nucleotides (adenylic, guanylic, cytidylic, and uridylic acid) or by the use of the mixture of these four mononucleotides in equimolar proportion, simulating the composition of tetranucleotides. Guanylic and uridylic acids were split at the highest rate, which agrees with the findings of others[8, 28] using tissue extracts. Desoxyribo-cytidylic acid was dephosphorylated by CSF's, like the pentose nucleotides.

Table V shows the results of simultaneous assays of nucleotidases and alkaline and acid phosphatases acting on the appropriate substrates.

Usually there was close correspondence between the splitting of the various substrates; occasionally, however, nucleotidase appears to be a completely different enzyme as regard pH and temperature optimum. This is in accordance with the findings of Lehman-Echternacht.[22]

TABLE V. NUCLEOTIDASES, ALKALINE, AND ACID PHOSPHATASES DETERMINED SIMULTANEOUSLY (EXAMPLES)

DIAGNOSIS	CSF VOLUME	SUBSTRATE	pH	INCUBATION	INCREASE IN IP μG/10 ML.
Meningococcus meningitis	0.2 ml.	3-adenylic acid	9	16 hr. at 37° C.	0
Meningococcus meningitis	0.2 ml.	3-adenylic acid	8.43	16 hr. at 37° C.	0
Meningococcus meningitis	0.2 ml.	3-adenylic acid	7.5	16 hr. at 37° C.	21
Meningococcus meningitis	0.2 ml.	3-adenylic acid	5	16 hr. at 37° C.	0
Meningococcus meningitis	0.2 ml.	Glycerophosphate	10.9	16 hr. at 37° C.	0
Meningococcus meningitis	0.2 ml.	Glycerophosphate	5	16 hr. at 37° C.	0
E. coli meningitis	0.2 ml.	3-cytidylic acid	9	16 hr. at 37° C.	2
E. coli meningitis	0.2 ml.	3-cytidylic acid	7.5	16 hr. at 37° C.	8
E. coli meningitis	0.2 ml.	Glycerophosphate	10.9	16 hr. at 37° C.	14
E. coli meningitis	0.2 ml.	Glycerophosphate	7.5	16 hr. at 37° C.	0
Staphylococcal meningitis	0.2 ml.	3-adenylic acid	9	4 hr. at 37° C.	0
Staphylococcal meningitis	0.2 ml.	3-adenylic acid	7.5	4 hr. at 37° C.	6
Pneumococcal meningitis	0.3 ml.	3-adenylic acid	9	16 hr. at 37° C.	14
Pneumococcal meningitis	0.3 ml.	5-adenylic acid	8.45	16 hr. at 37° C.	50
Pneumococcal meningitis	0.3 ml.	Glycerophosphate	10.9	16 hr. at 37° C.	21
Pneumococcal meningitis	0.3 ml.	Glycerophosphate	5	16 hr. at 37° C.	22

Magnesium activation usually enhances the dephosphorylation of NA and of nucleotides. A nonspecific depolymerizing effect of the Mg ion has to be taken into account,[8, 19] particularly during long incubation, as required in our experiments. This fact, however, does not influence the results directly, since the magnesium salt does not cause dephosphorylation in the molarity used.

The highest values ever obtained of all the dephosphorylating enzymes in the CSF were found with 5-nucleotides (muscle adenylic acid and inosinic acid). The 5-nucleotidase responsible for this is quite frequently demonstrable in the CSF and in our experience it was the only phosphatase present in amounts comparable to those in tissue and organ extracts or homogenates.* The increased activity at pH 7.5 exceptionally encountered (Table V) may be due to the presence of this enzyme or of specific 3-nucleotidases.[22]

As a rule, a linearity of nucleotidase activity in relation to CSF volume was observed. The enzymes were active in wide pH range, from 3 to 10.9. Temperature optimum was around 37° C.; prolonged incubation above this temperature had a deleterious effect on the nucleotidases and phosphatases, except 5-nucleotidase. The relative thermostability observed in some instances is due to the presence of the latter. Borate buffer partially inhibited the dephosphorylating enzymes but Veronal-acetate buffer gave optimal results. Deep-freezing, thawing, and storage at -25° C. caused an appreciable loss in activity of 3-nucleotidases and phosphatases, but had less adverse effect on diesterases, if not often repeated.

*To be published.

DISCUSSION

Enzymic dephosphorylation of a polymerized NA by CSF occurs only if nucleases and nucleotidases are simultaneously present and acting consecutively. The rate of IP production is similar to that found with nuclease-predigested NA or nucleotide substrate; therefore we could assume that oligonucleotides and nucleotides, already present or recently formed, are dephosphorylated. This is in agreement with the concept that nucleases liberate only oligonucleotides[4, 8, 12, 19, 20, 21] and that nonspecific diesterases[9, 11, 23, 30, 31] and phosphomonoesterases[6, 25, 30] are responsible for the hydrolysis of smaller molecular fragments. PNA was more frequently dephosphorylated, because RNA-se[14, 18] was more often present in the CSF than DNA-se,[15] and because PNA is more labile in an alkaline milieu, undergoing spontaneous depolymerization more easily.[8, 19] During the study of lecithinases we detected nonspecific diesterases in the CSF.[17] It may be possible that they are responsible for the observed splitting of predigested NA and of pure oligonucleotides.

The discrepancy observed between nucleotidase and phosphatase activation in some assays may be caused by the presence of either specific 3-nucleotidase[22] or 5-nucleotidase,[6] or both. Our findings concerning phosphatases agree in general with the results of Colling and Rossiter[3] who investigated these enzymes in the CSF's of similar conditions. They found a significant increase of acid and alkaline phosphatase in poliomyelitis and meningitis. They did not investigate the splitting of NA and nucleotides.

Bodian and Mellors[2] assayed histochemically the phosphatases in regen-

erating motor neurons of monkey spinal cord and found an increase of acid phosphatase activity. Bodian and associates[1] were not able to reproduce the same findings biochemically, but they found a tenfold increase of acid phosphatase activity in the regenerating peripheral nerve stump. These writers also mention the use of NA and nucleotide substrates.

The results obtained with poliomyelitis specimens during this work, especially against PNA and its derivatives, are significant and are in agreement with our previous findings,[14, 15, 16, 17, 18] suggesting an enhanced PNA metabolism in this condition. The origin of the enzymes was not systematically investigated during this study but most of the active CSF's were found in acute inflammatory conditions; however, no strict correlation was apparent with the cell count in polio specimens.

Only relative activity of the enzymes in CSF could be demonstrated. None were comparable in strength to concentrated or crystalline enzyme preparations except the 5-nucleotidases. This factor, inherent in the dilute nature of the CSF and aggravated by the small amount of CSF available, necessitated the long period of incubation.

SUMMARY AND CONCLUSIONS

Dephosphorylation of NA occurs when incubated under the conditions described. PNA was attacked most frequently (94 per cent) by CSF's of polio patients. The second most active group was the meningitides, followed by syphilis and miscellaneous neurological samples.

DNA was more resistant to dephosphorylation. The highest activity against this substrate was found in the syphilis group. Polio and meningitis specimens exhibited activity only in about 48 per cent of the cases.

There is definite correlation between nuclease activity and dephosphorylation in the PNA series. The degree of IP release is higher where high nuclease activity precedes the action of dephosphorylases. The ferment systems responsible are nonspecific diesterases, 3-nucleotidases, 5-nucleotidases, acid and alkaline monoesterases, demonstrated and illustrated.

The significance of these findings is that they elucidate a further step in the enzymic hydrolysis of NA in the CSF. The high rate of dephosphorylation of PNA by polio samples is important because it sheds more light on an intensified PNA metabolism in the central nervous system during this disease.

I express my profound gratitude to the late Dr. D. T. Fraser for his advice and criticism, and to the staffs of the Toronto hospitals for supplying CSF samples. Special thanks are due to Mrs. Katalin Vlossak and to Lajos Szendy for their technical assistance.

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SECONDARY HYPERSPLENISM OCCURRING IN A SEVEN-MONTH-OLD INFANT WITH THALASSEMIA MAJOR

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SECONDARY hypersplenism has been described in association with splenomegaly from a variety of causes, both mechanical and hematologic, such as Gaucher's disease, sarcoidosis, tuberculosis of the spleen, Hodgkin's disease, portal hypertension and thalassemia major. The hypersplenic activity may manifest itself as excessive destruction of the erythrocytes, platelets, or neutrophils or any combination thereof. Although an increased rate of destruction of normal erythrocytes has been described in patients with thalassemia major, this has not been reported previously in young infants. Moreover, published reports indicate that the presence of both hemolytic and thrombocytopenic manifestations of hypersplenism is rare. The present report concerns a patient with thalassemia in whom, probably at the age of 5 months and certainly by 7 months, an enlarged spleen produced a severe anemia with a shortened survival time for normal red blood cells and a mild but definite thrombocytopenia.

CASE REPORT

C. M., a white male infant of Greek extraction, was admitted to St. Christopher's Hospital for Children on Aug. 26, 1954, at the age of 7 months. He had been hospitalized elsewhere at the age of 4 months because of a perianal abscess, which was successfully treated. At this time it was demonstrated that he had thalassemia major, his hemoglobin being 4.6 grams per 100 c.c. and his red blood cells 2,310,000 per cubic millimeter. He received a transfusion of 150 c.c. of packed red blood cells, following which his hemoglobin level rose to 10.1 grams per 100 c.c.; he was discharged on June 6, 1954. By July 6 his hemoglobin level had fallen to 6.5 grams per cent, necessitating a second transfusion of packed red blood cells. A third transfusion was also given on August 2, at which time his hemoglobin was 5.4 grams per cent. By August 26, only twenty-four days after his last transfusion, his hemoglobin had again fallen to 4.5 grams per cent. Owing to the persistent severe anemia necessitating transfusions more frequently than would be expected in the usual patient with Cooley's anemia, he was transferred to St. Christopher's Hospital for Children for further study.

The infant's delivery had been spontaneous at 9 months' gestation; his weight at birth was 8 pounds 6 ounces. He had eaten poorly since 2 months of age, his gain in weight had not been satisfactory, and he had always been excessively fussy.

The family history failed to reveal anemia in any other member of the family, but the findings of thalassemia minor were present in both parents, with hypochromia, target cells, and poikilocytosis.

Physical examination revealed a thin, very pale, hypoactive but very irritable infant with an olive-hued complexion. His height was 27½ inches

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and his weight, 14 pounds, each being below the third percentile for his age. A grade II systolic murmur was audible at the base of the heart, the abdomen was protuberant, and the edge of the liver was palpable 2 inches below the right costal margin; the tip of the spleen was 2½ inches below the left costal margin in the anterior axillary line. The hemoglobin level at the time of admission was 4.5 grams per cent; the erythrocyte count was 2,140,000 with 14 per cent reticulocytes, and that of the leukocytes was 16,000 per cubic millimeter, with a normal differential distribution. The erythrocytes revealed the typical findings of thalassemia major; viz., severe hypochromia, anisocytosis, poikilocytosis, and numerous macrocytes. Target cells constituted approximately 10 per cent of the erythrocytes. No nucleated red blood cells were seen. The initial platelet count was 104,000 per cubic millimeter by the direct method; subsequent platelet determinations ranged between 60,000 and 160,000. The patient's blood type was A, D positive. The direct serum bilirubin level was 0.85 mg. per cent, with a total of 1.7 mg. per cent.

Studies on the parents confirmed the previous diagnosis of thalassemia minor.

Owing to the severity of the anemia, the frequency with which transfusions were necessary, the reduced number of platelets and the abnormally enlarged spleen, secondary hypersplenism was suspected and studies performed to test this diagnostic possibility.

The patient was transfused with 140 c.c. of type O, D positive erythrocytes. The survival of these cells was followed by differential agglutination methods and blood volume determinations. The method of Mollison and Young[9] was employed for differential agglutination, using anti-A antiserum to agglutinate the cells of the patient. The pretransfusion control determination of unagglutinated cells using this serum with the patient's cells was 46,000 per cubic millimeter. This number was subtracted from each determination in computing the survival of the transfused cells. The blood volume was determined using the Evans blue dye method with a separate standard prepared in the patient's own plasma prior to each determination. Hematocrit determinations were made on venous blood using the capillary method of Strumia and associates.[10] A correction factor of .87 was applied to the observed hematocrit to correct for both trapped plasma in the red cell mass and the body/venous hematocrit

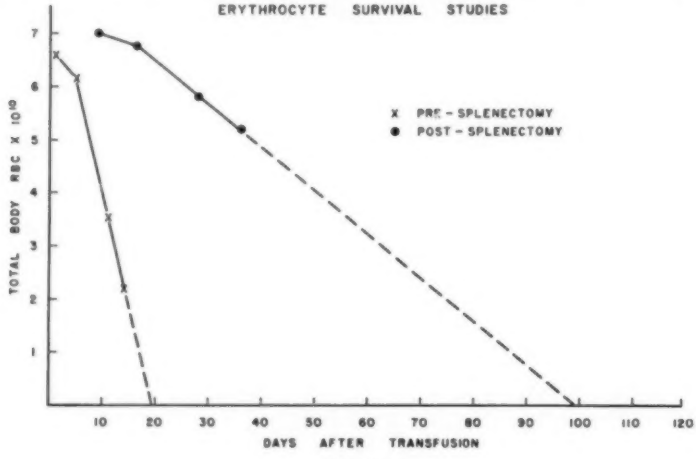

Fig. 1.

difference in determining the blood volume. The results of this study are presented in Fig. 1 and show, by extrapolation, a survival time for normal transfused cells of eighteen to twenty days. This is far shorter than normal and is in agreement with the clinical impression of hypersplenism.

In addition to the excessive destruction of erythrocytes, it was believed that there was excessive destruction of the platelets. The platelet levels have been noted; they were always below the lowest normal levels for this laboratory. The patient developed petechiae following very slight trauma, and on one occasion petechiae were present on the trunk and legs in the absence of known trauma. A positive tourniquet test could be obtained when the platelets were at their lowest levels, and at this time evidence of deficient prothrombin consumption was obtained by means of the prothrombin consumption test of Quick, although clot retraction was normal. Marrow aspirated from the tibia contained a normal number of megakaryocytes as estimated on the smear; all of the megakaryocytes were "mature," normally granular, and productive of platelets. There was erythroid hyperplasia of the marrow with an E:M ratio of 4.3:1.

From these observations it was concluded that this patient had severe secondary hypersplenism and would benefit from splenectomy. This was performed on Sept. 13, 1954, by Dr. Samuel Cresson. The postoperative course was uneventful. The platelets rose to 370,000 per cubic millimeter on the fourth postoperative day and have remained above 200,000 per cubic millimeter to the present. A postoperative survival study of normal erythrocytes transfused into the patient, performed as in the preoperative studies, revealed a survival time of 110 days. This test was performed as an outpatient three weeks after operation, and, since the patient did not always return as requested, the number and spacing of the determinations is less than optimum. Nevertheless, the slope of the determination is such as to indicate an essentially normal survival time. In addition, the hemoglobin level remained between 7.2 and 7.6 grams per cent during the first four postoperative months. Since he had gained 7 pounds, shown a good developmental pattern, eaten tremendously, and had not been irritable nor easily fatigued, no transfusions were given during this period. At the end of four months his hemoglobin level fell to 6.4 grams, he became lethargic and irritable, and a transfusion was deemed advisable. At this frequency, he will require a transfusion every three to four months, a marked improvement over the previous three- to four-week interval between transfusions.

DISCUSSION

The value of splenectomy in thalassemia has not been realized until recently. Following the early descriptions of the disease, there were reports of clinical improvement following splenectomy, the spleen usually being removed because of its large size and the associated mechanical difficulty. No erythrocyte survival studies are available in these early reports, although the possibility of hypersplenism is frequently mentioned. Low levels of platelets are recorded in some of the patients, with a rise in platelets following operation. Zuelzer and others[3, 4] have demonstrated normal survival times for normal erythrocytes transfused into patients with thalassemia. These findings may have reduced the incidence of splenectomy in this disease since it is apparent that in the usual patient the defect is in the cells of the patient and not the result of increased destruction of normal erythrocytes. Lichtman and co-workers[5] were the first to call attention to the extracorpuscular defect which may occur in patients with thalassemia with severe splenomegaly and to study the

survival of normal erythrocytes before and after splenectomy. The findings of Lichtman and associates[5] have been confirmed by Smith and Shulman.[7] Insofar as we have been able to determine, however, the patient reported here is the youngest patient with Cooley's anemia in whom a decreased survival time for normal erythrocytes has been demonstrated; indeed, the statement has been made that this complication is one of late childhood or adult life. The assumption is made, although not proved, that this secondary hemolytic mechanism also affects the patient's own cells with a resultant double burden of hemolysis. The gratifying clinical and laboratory results achieved in this patient indicate that splenectomy should be considered when the anemia of Cooley's anemia is more severe than expected or when transfusions are necessary at intervals of more than six to eight weeks. Splenectomy should certainly be performed when a shortened survival time for normal cells transfused into the patient can be demonstrated. The occurrence of thrombocytopenia in the present infant was additional evidence of hypersplenism; this manifestation may be the only evidence of the increased activity of the spleen in some patients with thalassemia and secondary hypersplenism.

SUMMARY

A patient is described with thalassemia and secondary hypersplenism at 5 months of age. Shortened survival time for transfused normal erythrocytes, extremely limited benefit from transfusions, and thrombocytopenia were present.

Following splenectomy the survival time for transfused normal cells was normal, the platelets rose to above 200,000 per cubic millimeter, and there was striking clinical improvement.

CONCLUSIONS

1. Secondary hypersplenism may occur in patients with Cooley's anemia at any age.

2. Patients with this condition in whom hypersplenism can be proved will often benefit from splenectomy.

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HYPERTRICHOSIS OCCURRING IN ASSOCIATION WITH DILANTIN THERAPY

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THE term "hirsutism" has been used by Wilkins[1] to denote excessive growth of sexual hair of a masculine pattern, while "hypertrichosis" has been applied to the more general growth of excessive body hair.

In children with the adrenogenital syndrome or male sexual precocity, hair growth begins at an early age over the pubis and in the axilla and later may extend onto the abdomen, chest, face, and extremities. It is associated with excessive secretion of androgen and is accompanied by other signs of virilism. In women with the adrenogenital syndrome or virilizing tumor of the ovary, such as arrhenoblastoma[2] or with the Stein-Leventhal syndrome, there is a similar masculine distribution of excessive hair, but masculine hirsutism may occur also as a constitutional trait in the absence of an endocrinopathy.[3, 4] In Cushing's syndrome, or after the administration of large amounts of cortisone, the hair distribution may be of a less distinctly sexual pattern often beginning on the forehead.

Excessive growth of sexual hair should be distinguished from more generalized hypertrichosis or that confined to local areas of the body. In young infants and children there may be idiopathic hypertrichosis, particularly over the shoulders, back, and extremities. Hypertrichosis has been reported in many chronic debilitating diseases such as celiac syndrome and tuberculosis and after the administration of streptomycin.[5, 6] Localized growth of hair sometimes occurs over nevi, with dermatomyositis, after roentgen therapy,[7] or the application of plaster casts.

Fig. 1.

The purpose of this paper is to report the occurrence of hypertrichosis in sixteen epileptic children who were treated with Dilantin.

These patients (fourteen girls and two boys) varied in age from 3 to 14 years. The hypertrichosis appeared between two and three months after the initiation of Dilantin therapy. It

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occurred predominantly on the extensor surfaces of the extremities; in several patients it appeared also on the trunk and face. The distribution of the hair did not simulate a sex pattern in any case. Three patients, in whom the hypertrichosis had raised a suspicion of an endocrine disturbance, were studied by Dr. Lawson Wilkins, who found no evidence of hormonal disturbance or elevation of the urinary 17-ketosteroids.

In twelve of these sixteen patients the hypertrichosis disappeared within one year after the withdrawal of the Dilantin. It has persisted in the remaining four who have been maintained on the drug. The growth of hair was related neither to the dosage of Dilantin nor to the type of epilepsy.

Fig. 1 shows the excessive growth of hair on the anterior surfaces of the thighs of a 14-year-old girl who has been receiving 100 mg. of Dilantin three times a day for the past three years. Coarse hair had been present on the lower legs but had been shaven for cosmetic purposes. The hypertrichosis was generalized, but the patient allowed us to photograph only her legs.

SUMMARY

The occurrence of hypertrichosis in sixteen epileptic patients treated with Dilantin is reported.

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DISPARITY IN THE CARDIAC STATUS OF MONOZYGOTIC TWINS

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IT IS probably true that one must exercise caution when making allusions to the differences in inheritance involving identical twins. The concept that "identical twins" must be geotypically identical and suffer from the same disturbances has been discussed by Wade.[1] This writer pointed out that the genetic mechanism involved might be of low penetration and require an environmental disturbance as the trigger action necessary for its expression.

Newman,[2] in discussing the mechanism of the mirror image, has stated that where twinning occurs at the stage of late gastrulation (when differentiation of the right and left sides has already taken place) that reversed symmetry might occur as in dextrocardia as part of a situs inversus.

There might be another mechanism of importance involved here in this rather profound sequence of twins variables—the feature of the embryology of *hollow organs* which, in addition to the ordinary growth and development characteristics, have the added mechanism of rotation or torsion. This might as well apply to the gastrointestinal tract as to the heart.

CASE REPORT

David and Donald G. were born of a primiparous mother on Nov. 9, 1947. David (the affected twin) weighed 7 pounds 14 ounces, was 53½ centimeters long, and had an occipitofrontal circumference of 33 centimeters. He evidenced no cardiac enlargement, but a loud systolic murmur was heard over the entire precordium with loudest intensity at the mid-sternum. Donald (the normal twin) weighed 7 pounds 2 ounces, was 53 centimeters long, and had an occipitofrontal head circumference of 34 centimeters. The only other difference between the two babies was the presence of a small sebaceous cyst on David's nose.

The placenta showed no evidence of separation into two portions and the two umbilical cords were attached to the placenta in close proximity.

The infants were breast fed and gained rapidly. At the age of one month, David weighed 10 pounds, while Donald weighed 9¾ pounds. The babies developed bilateral hydrocele at the age of 5 weeks. The infants weighed 15¾ pounds at the age of 3 months, and there was no essential difference in their physical activity. They had remained well except for coryza. The central incisors were apparent in each infant at the age of 5 months. Each child weighed 33 pounds at the age of 2 years. There was little to distinguish the two boys except for the nasal cyst which was later surgically removed.

Fluoroscopy of the chest (David, Dec. 13, 1947) showed "extension of the apex of the heart into the right chest with a convexity building sharply from the left base into the left lung field. The pulsations over the right lower heart had a very active fluttering activity, whereas those over the left base were more forceful and deep

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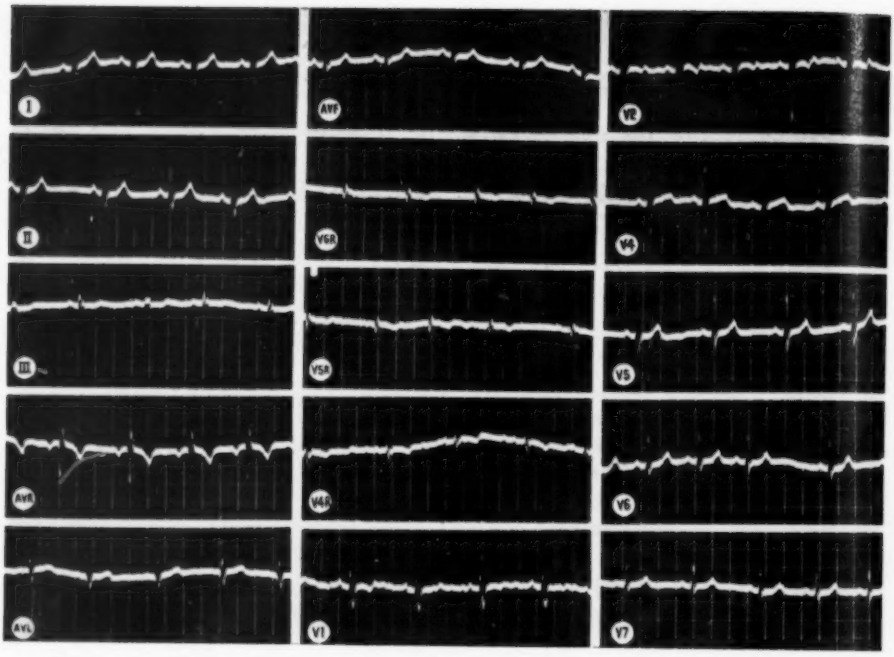

Fig. 1.—An electrocardiogram of the unaffected twin. Record made on April 15, 1954.

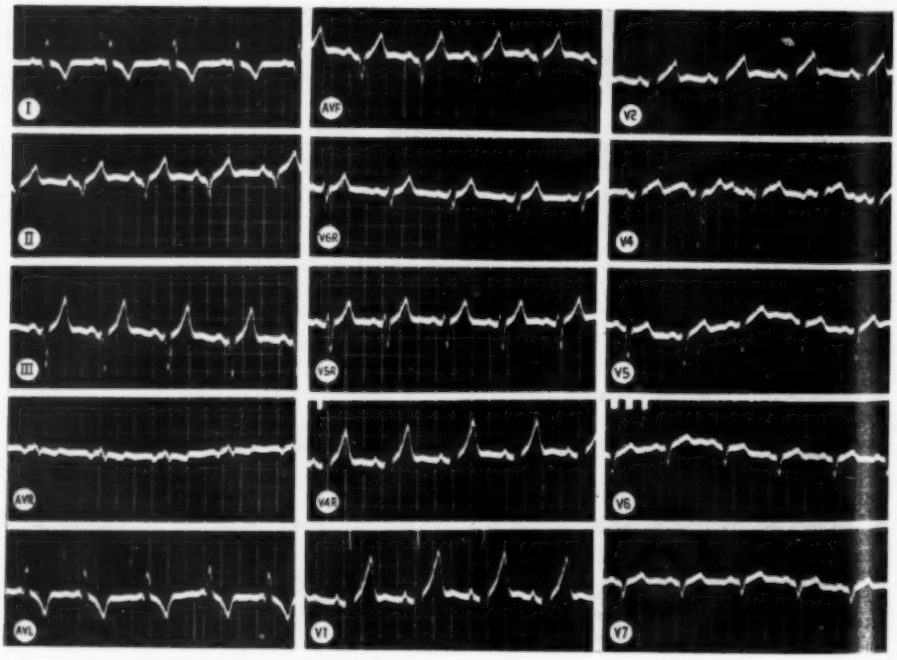

Fig. 2.—An electrocardiogram of the affected twin. Record made on April 15, 1954.

with slower rhythm. A deep indentation of the left side at the base corresponding to the large convexity in the cardiac border marked the course of the esophagus. Obliteration of the anterior cardiac space is present."

Fluoroscopy, Jan. 10, 1948: "There is the presence of asymmetrical widening of the base of the heart with a convex density projecting into the superior paramediastinal portion of the left chest with the apex of the heart extending into the right side of the thorax. The middle cardiac segment on the right is abnormal as characterized by the convex density filling this area. If this is a true dextrocardia, this fullness in the middle cardiac segment on the right may correspond to an enlarged pulmonary conus. Again, the configuration resembles the tetralogy of Fallot in reverse except that there is no sharp indentation in the region occupied by the pulmonary conus as is found in cases with pulmonic stenosis." This patient showed no clinical signs of pulmonic stenosis, so such a finding would be unexpected.

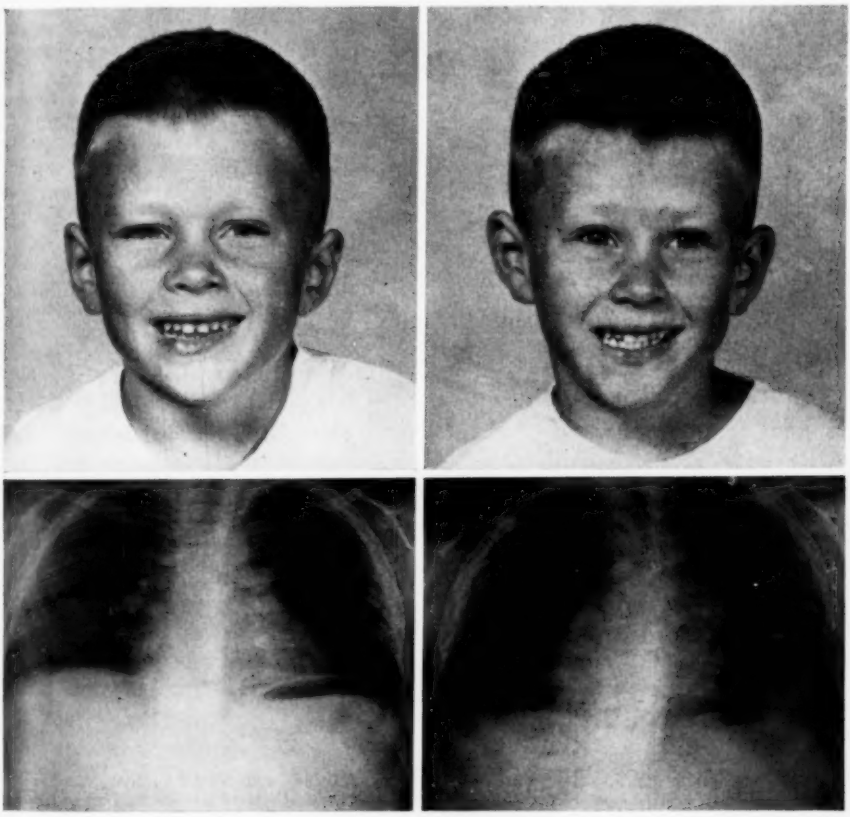

Fig. 3.—Photographs and chest x-rays of the two boys. David's photograph and chest film are on the right.

Repeated examinations of the two boys continued to show no essential change in cardiac findings. David's murmur was fully systolic, with greatest intensity at the right border of the upper sternum. Pulmonary conges-

tion did not occur and the liver was never enlarged. The blood pressure was 115/70 in both upper extremities. The child's activities were always as strenuous as the twin brother's.

The original cardiogram was taken on Jan. 12, 1948, and the following interpretation given: Leads I and III did not equal Lead II. The QRS complex in Lead I consisted of a small Q and a tall R. If Lead I is examined in its mirror image, Lead I plus Lead III would not equal Lead II; hence, this electrocardiogram represented a mirror image of the ventricles. The P wave was upright in Lead I. This was the expected finding in a so-called mixed type of isolated dextrocardia. In other words, the auricles remained in a relatively normal position as did the sinus node, whereas the relationship of the limb leads to each other suggested pulmonic ventricular strain or what in a normal heart would be a right-heart strain (a deep S in Lead I).

A complete electrocardiogram was taken of both boys at 6½ years of age. The interpretation confirmed the belief that we were dealing with a mixed isolated dextrocardia, that is, a mirror-image position of the ventricles and a pivotal position of the auricles which allows the sinus node to remain in a normal position in regard to the auricles. This type of electrocardiogram has been associated with a pulmonary stenosis and usually a large septal defect. In fact, most of these children have a functionally single ventricle.

The T wave in Lead I was inverted. The reason that the QRS was not inverted was because of the pulmonic ventricle being enlarged. If the QRS was turned upside down (its mirror image), one would see the deep S wave ordinarily associated with a right-heart strain in a normally placed heart. The P wave was upright because the auricles did not participate in the mirror image dextrocardia.

The final important interpretation attached to the electrocardiogram was:

1. Sinus rhythm.
2. Dextrocardia of the mixed type, mirror image position of the ventricles with the auricles in a relatively normal position.
3. Pulmonic ventricular strain (the equivalent of right-heart strain in the normally placed heart).
4. The type of record usually seen in isolated dextrocardia associated with pulmonary stenosis.

A follow-up on the two boys when they were 7 years of age was of interest. The weight of the two children was identical (55 pounds). Donald was 47⅝ inches and David 47¼ inches tall. Donald was absolutely right-handed, while David was predominantly left-handed but could manage with his right hand. Donald excelled slightly in athletics and David was slightly more advanced academically.

CONCLUSIONS

It is felt that the criteria of Newman[2] have been satisfied in establishing these twins as monozygotic.

The disparity in the cardiac status of identical twins has been previously described.[1, 3] Debreuil-Chambardel[3] described dextrocardia in one of conjoined twins (*psodyme*).

The progress of my patient, David G., has been reassuring. The prognosis in isolated dextrocardia is very poor, most deaths occurring during the first year.

I am indebted to Dr. Robert A. Miller (Children's Memorial Hospital, Chicago, Ill.) for his electrocardiographic interpretations.

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THE TREATMENT OF ECZEMA IN INFANTS AND CHILDREN

PART II

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SEBORRHEIC DERMATITIS

SEBORRHEIC dermatitis is more common in babies under 4 months of age than it is in older children. It is most frequently seen in fat babies, and in looking over the records from my office files of twenty-six babies in whom I had made this diagnosis, on sixteen of the records I had put down a special note that the baby was thriving and very fat. In another consecutive series of 100 eczematous babies under 2 years of age, the diagnosis of seborrheic dermatitis had been made in eighteen.

Seborrheic dermatitis often begins with cradle cap, a superficial scaly eruption on the cheeks and intertrigo of the axillae, groins, and neck, and sometimes around the umbilicus. In many patients the trouble goes no further than this. In some, lesions develop on the trunk—the arms and legs are not likely to be involved. Seborrheic dermatitis is essentially a disease of scaling on an inflammatory base; vesiculation is not present, nor is oozing, unless there has been a good deal of rubbing. The lesions on the trunk begin as small, light pink spots, which are covered with yellowish scales. The scales may or may not be greasy. These spots enlarge and coalesce to form still larger areas, which may sometimes be sheetlike in character. There is often clearing in the center, and the margins are sharp. In some cases there may be a more severe degree of inflammatory reaction, and the entire skin surface may be covered with large plaquelike scales; seborrheic dermatitis has taken on the characteristics of Leiner's disease (see below).

In older children intertrigo and cradle cap are not so prominent as in babies, and Leiner's disease does not occur. As a rule, seborrheic dermatitis itches but little, there is no eosinophilia, skin tests are negative, and unless complicated by atopic dermatitis it is not associated with asthma or hay fever. It does, however, in infancy bear some poorly understood relationship to atopic dermatitis, and often precedes it. Some babies who have seborrheic dermatitis at the third or fourth month are cured of it with proper treatment—there is no recurrence and they develop no atopic dermatitis, hay fever, or asthma. In others, characteristic atopic dermatitis, with vesiculation, severe itching, and positive skin tests gradually develop, so seborrheic dermatitis, although not primarily an allergic disease, can and does occur in allergic infants.

The cause of seborrheic dermatitis is not well understood. Some have thought that it is due to infection with a yeastlike organism (pityrosporon of Malassez), others that it is from overactivity of the sebaceous glands, others

Fig. 1.—Seborrheic dermatitis. The lesions are "nummular" in shape, but very different in color and appearance from those seen in nummular eczema. Note piling up of scales and clearing in centers of some lesions.

Fig. 2.—Seborrheic dermatitis.

Fig. 3.—Same patient as in Fig. 2, after treatment.

that it has nothing to do with the sebaceous glands, but that it is caused by a deposition of too much fat in the skin from eating too much fat, still others that the cause is lack of a special dietary factor which is contained in liver, casein, and some vegetables, particularly carrots. It seems possible that all these factors may be operative. The sharply margined lesions certainly suggest infection with a yeastlike fungus, and they respond well to ammoniated mercury or sulfur ointment; in adults seborrheic dermatitis often occurs in places where there are abundant sebaceous glands (the sides of the nose and front of the chest), and in infancy it is undoubtedly most likely to occur in fat babies who are overfed with milk fat, and a diet low in fat and high in casein is efficient therapeutically.

Treatment is efficient: it is combined local and dietetic.

The Scalp.—If local treatment is to do any good, the hair must be cut as short as possible.

A. *The Dry Type With Small Scales:* First thickly apply the following salve for three days. Rub it in well, and cover the head with a cheap cotton cap.

Ac. salicylic gr. xx
Petroleum jelly ℥ iv

On the fourth day scrape out with a fine comb as much of the scale as possible. Shampoo with pHisoHex or a mild soap. Then apply Pragmatar ointment.* This consists of coal tar, sulfur, and salicylic acid. It is a fairly strong ointment, but most scalps tolerate it. Use this for three days, shampoo again, then leave the scalp alone for three days. Repeat the treatment, and keep up this schedule as long as necessary.

B. *Crusted Type:* Here there is a foul, piled-up accumulation of yellow crusts and scales, with the hair matted down in it, and underneath all this an inflamed scalp. It is necessary to do away with this corruption and get down to bedrock before any good can be done. It is not possible to do a good job of hair cutting until the whole mess has been softened up. The best way to do it is with continual dressings of thick gauze packs wet with normal saline solution, kept on by a tightly fitting cap. After about two days of this treatment the hair can be cut, and the scalp gently scraped and washed with pHisoHex. This usually leaves a

Fig. 4.—A bad scalp, much crusted and with matted-down hair.

*Smith, Kline & French Laboratories, Philadelphia.

pretty much reddened, inflamed surface. If there are oozy places the oozing must be stopped. If there are not many and they are small, wet dressings of ¼ per cent silver nitrate solution can be used. If the whole head is involved it is best to use Burow's solution (1 tablespoonful to 1 glass of water). Then boric or zinc oxide ointment is applied for a few days, and when the inflammation has calmed down somewhat, proceed with the Pragmatar ointment as in the dry type. If there is pustulation, neomycin, bacitracin, or erythromycin ointment should be used, plus an antibiotic internally.

Intertrigo.—For intertrigo, salves are of no value except possibly hydrocortisone ointment, and often do more harm than good. Lotions are better.

My favorites are:

(1) Burow's solution ℥iv
Zinc oxide
Talc aa ℥ i
Glycerin ℥ vi
Lime water ad ℥ iv
(2) Aqueous solution of gentian violet 1%
(3) Silver nitrate solution 0.25%

Fig. 5.—Seborrheic dermatitis. Local treatment: tar paste or sulfur and salicylic acid ointment.

It is also desirable, if possible, to prevent the skin surfaces of the creases from coming together, and little rolls of absorbent cotton can usually be kept on pretty well in the groins, and in the creases of the neck.

Lesions on the Body.—For lesions on the body, crude coal tar paste, ammoniated mercury, salicylic acid and sulfur, Pragmatar, or Vioform ointments are excellent.

*(1) Crude coal tar ʒ i
Zinc oxide ʒ ii
Starch ʒ iv
Petroleum jelly ad ʒ ii

(2) Ammoniated mercury ointment U.S.P. 3%

(3) Ac. salicylic,
Precipitated sulfur āā gr. xx
Petroleum jelly ʒ ii

(4) Pragmatar ointment

(5) Vioform 2% in petroleum jelly or in Lassar's paste, or Vioform cream 3%†

Feeding.—The diet is important. The milk formula should be low in fat and sugar, and high in casein, about as follows:

Pour off the top 4 oz. from a quart of milk and use it for something else.

The formula is

28 oz. milk
6 oz. water
2 level tablespoonfuls of Karo syrup or Dextri-Maltose‡
4 level tablespoonfuls of Casec.‡

Cook in a double boiler for ½ hour to make a smooth gruel and add enough water to replace what has boiled away.

Soybean foods, which are used now by so many pediatricians for practically every baby who has any skin rash whatsoever, are not indicated.

It is probably a good plan to give multiple vitamin B_{12}§ drops, and finely ground liver. I am not sure whether or not these really do any good but they can do no harm, and have been highly recommended by some.

*For other tar ointments, see section on atopic dermatitis.

†Ciba Pharmaceutical Products, Inc., Summit, N. J.

‡Mead Johnson & Company, Evansville, Ind.

§Multi-Beta B_{12} drops, White Laboratories, Kenilworth, N. J.

The results of treatment in seborrheic dermatitis, provided there is no allergy along with it, are usually very satisfactory.

Leiner's Disease

This is probably a generalized and greatly intensified seborrheic dermatitis, but has certain features peculiar to itself. It was first described in 1908 by Leiner, a Viennese dermatologist, as follows: "A slight inflammation of the whole cutis, a desquamation of the epidermis, and a seborrhoea of the scalp."[1] In his first report there were forty-one cases; fifteen of the patients died. It has been said by some that Leiner's disease is the same as Ritter's disease. I am doubtful of this, for it looks nothing like Ritter's disease (see Figs. 6, 7 and 8). Furthermore, Ritter's disease is a disorder of the newborn infant. Leiner's disease occurs in young infants (first 3 months) but not in the newborn period (first 3 weeks).

This was at one time a common disease in Europe—it is said to be infrequent there now. It has never been common in this country. It may begin much as seborrheic dermatitis does, with intertrigo, cradle cap, then gradual extension, until the whole skin surface, except the palms and soles, is involved, or it may begin with an acute eruption somewhat resembling measles, then rapid coalescence and scaling of the originally maculopapular lesions. In uncomplicated cases there is little itching, no eosinophilia, no marked general glandular enlargement, and no allergic antibodies to be found in the blood. This applies to the classical type which was originally described by Leiner, and later so carefully

[1]Brit. J. Child. Dis. 5: 244, 1908.

studied by Ernst Moro at Heidelberg.[2] In this country, mixed forms, showing some of the clinical features of both Leiner's disease and of atopic dermatitis, are not uncommon. (See atopic erythroderma.) I expect that the answer to these mixed forms of atopic and seborrheic dermatitis is that the process which causes seborrheic dermatitis occurs sometimes in babies who are allergic, sometimes in those who are not. In the first group, the skin appearance suggests both atopic and seborrheic dermatitis; in the second, classical and uncomplicated seborrheic dermatitis.

Fig. 6.—Ritter's disease. Note loose adherence and large size of scales, very different from Leiner's disease.

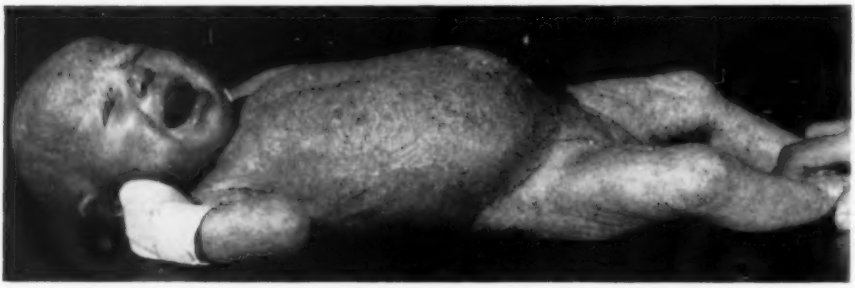

Fig. 7.—Leiner's disease. Note close adherence of scales.

[2]Moro, Ernst: Ekzema Infantum und Dermatitis Seborrhoides, Berlin, 1932, Julius Springer.

Diarrhea is common in Leiner's disease and is often serious. Secondary infection is frequent; nutrition may become poor. There is often a low serum protein with consequent edema, probably caused by loss of nitrogen from the body in the form of scales (keratin). There is evidently some abnormal metabolic process going on which interferes with the normal keratinization process of the epidermis.

I have seen patients with classical Leiner's disease (the baby in Fig. 7 was

Fig. 8.—Leiner's disease. (From Brennemann's Practice of Pediatrics, W. F. Prior Co., Inc.)

such) who recovered entirely in a few weeks and had no further trouble with the skin. I have seen others who looked in the beginning like those in the first group, but who developed general glandular enlargement, eosinophilia, blue feet, itching, transferable antibodies to egg white and to other food and environmental allergens—who took two years to recover from the dermatitis, and who later had hay fever or asthma.

Treatment.—The same diet as for seborrheic dermatitis is recommended, and plenty of it. These babies are poorly, and need food. For local treatment, only mild preparations should be used, such as petrolatum, or petrolatum with the addition of 5 grains of salicylic acid to the ounce.* The scalp is treated the same as in seborrheic dermatitis. These patients can be bathed—indeed it is better to bathe them, and probably better to wash them with pHisoHex than with soap. If they are in a hospital, and consequently exposed to all sorts of infection, they should be given an antibiotic. It may be necessary, if they become edematous, to use serum replacement therapy. Any young pediatrician who has passed the Pediatric Board examination knows so much more about this than I do that I would be ashamed to discuss it in detail. I have had no experience with cortisone in Leiner's disease.

Eczematous Fungus Infections

Twenty years ago I thought it was possible that secondary fungus infection might be important in atopic dermatitis, and that some other eczema-like eruptions in children which did not fit well into classification might be primarily caused by fungi. The two main groups of fungi which have been found to be of importance in eczema-like eruptions in adults are the trichophyton and the group of yeastlike fungi, particularly *Candida (Monilia) albicans.* Not being well versed in the intricacies of mycology, it seemed to me that I could probably learn more

*This salve, or any other containing an active drug, should not be used for long over the whole body. There is too much danger of absorption of toxic amounts of the drug.

about this question by doing skin tests than by making cultures or scrapings. Intracutaneous tests with trichophyton and Oidiomycin, which give the twenty-four-hour delayed tuberculin type of reaction, are quite reliable in indicating whether or not infection with the corresponding organism is or has been present, exactly comparable to the significance of a positive tuberculin test. I tested sixty eczematous infants and children, just as they came, without selecting any special type of eruption, with trichophyton 1 to 100. There were two doubtfully positive reactions. This showed pretty clearly that trichophyton infection either primary or secondary is unusual in eczema-like eruptions in children. "Ringworm," which is caused by a trichophyton, is, of course, common, but is not ordinarily classed as an eczema-like eruption, and is not likely to be confused with eczema. One hundred eczematous chil-

Fig. 9.—Moniliasis. Cured with 2 per cent gentian violet ointment. (From J. A. M. A. 103: 333, 1934.)

dren were tested with "Oidiomycin" 1 to 100, with fifteen for the most part strongly positive reactions. Most of these children who gave positive reactions showed three types of eruption:

1. Patchy, sharply margined rather superficial areas on the inner side of the thighs, and in the pubic region.

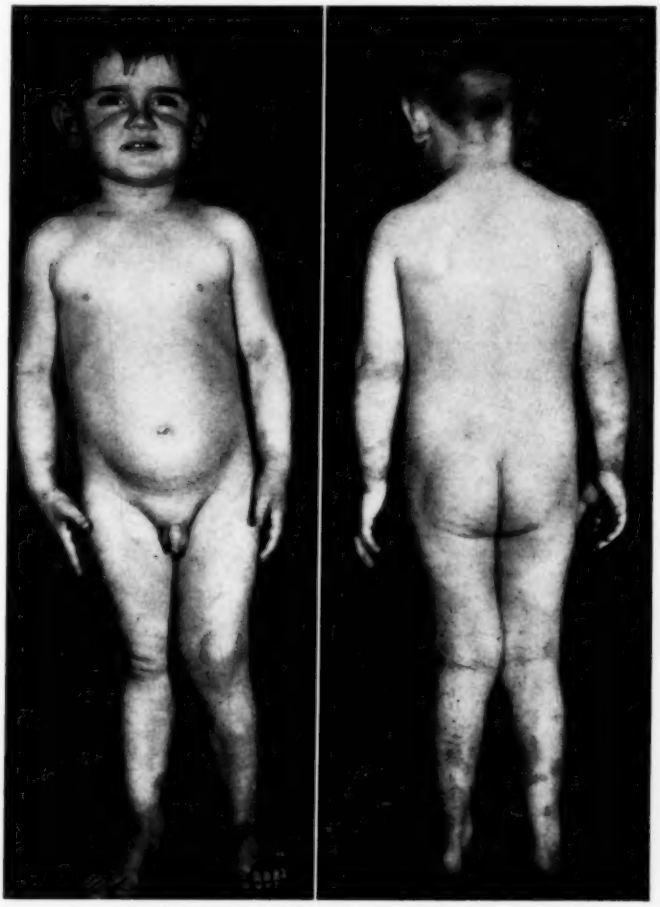

Fig. 10.—Same patient as in Fig. 9, after two weeks' treatment. (From J. A. M. A. 103: 333, 1934.)

2. The same sort of lesions on the trunk, which in some cases were extensive.

3. Scaly fingers, with involvement of the nails. In these patients, except for those who had finger and nail involvement, treatment with gentian violet was very satisfactory. (See Figs. 9 and 10.)

More recently, Dr. Henry Harris Perlman[3] of Philadelphia, who is not only a certified pediatrician but a certified dermatologist as well (I expect the only one of the species in existence), and who therefore knows a great deal more about mycology than

[3] J. PEDIAT. 34: 458, 1949.

Fig. 11.—Probably fungus infection. Not proved, but cured with antiparasitic treatment. (From Brennemann's Practice of Pediatrics.)

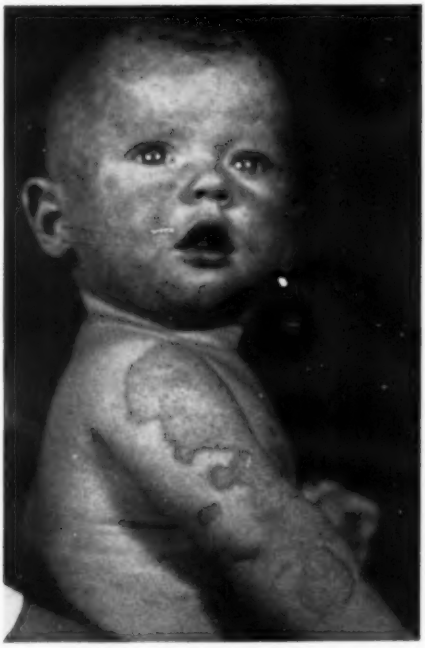

Fig. 12.—Probably fungus infection. Not proved. Cured with antiparasitic treatment.

I do, studied a series of sixty-eight cases of atopic dermatitis in children to determine whether or not fungi were complicating the situation. He found no pathogenic fungi. In this, his results agreed very well with mine so far as trichophyton is concerned, but not for monilia. A possible reason for this may be that he investigated only patients with atopic dermatitis. I took consecutive cases of any sort of eczematoid dermatitis. He, being a trained dermatologist, would have excluded eruptions which to him were obviously monilia infections. I did not.

Fig. 13.—Moniliasis. Note sharp borders. Also note extension to face. (From Brennemann's Practice of Pediatrics.)

In 1953, King, Walton, and Livingood[4] reported ten cases of proved trichophyton infection in infants under the age of 10 months. This was in a hot, damp climate (Southern Texas), and they were of the opinion that these infections might be more common in such a climate than elsewhere. They say nothing about the morphology of the eruptions, which is a pity. There is a picture, however, which looks almost exactly like the babies shown in Figs. 11 and 12. I treated these babies about twenty-five years ago and cured them both very easily with antiparasitic treatment because I thought their trouble *looked* like fungus infection; no cultures or scrapings were made.

In the last five years I have been much impressed with the increasing frequency of skin moniliasis in young infants under the age of 2 months. This often begins in the newborn period, around the anus and in the pubic region, and rapidly spreads, so that it may cover large areas, even invading the chest, neck, and face. These patches are of a beefy red color, usually with slight scaling. The edges are somewhat raised, with very sharp margins. There are usually, but not always, a number of small satellite lesions, from the size of a pea to that of a dime, which, in their turn, enlarge and fuse with the larger areas. There may be cracks with exudation in the larger patches, but I have not seen the vesicular or pustular lesions which have been so often described. There is little itching, and the general health of the baby is good.

Some of these babies have had oral thrush while in the hospital. The mothers of others have had a vaginal infection with *C. albicans* during preg-

[4]King, William C., Walton, Ida K., and Livingood, Clarence S.: Superficial Fungus Infection in Infants, Arch. Dermat & Syph. 68: No. 6, 1953.

nancy. Whether or not the increased incidence of monilia skin infection in infancy is due to wide use of broad spectrum antibiotics, I do not know. Newborn babies do not, as a rule, take antibiotics; perhaps some of the mothers have done so.

Diagnosis is made by the appearance of the skin or by cultures if one is in doubt. I do not think much of smears.

A good treatment is to paint the involved areas twice a day with a 2 per cent aqueous solution of gentian violet, or if the patches are much thickened, the gentian violet is used in 2 per cent strength in petrolatum and well rubbed in. Two per cent Vioform in petrolatum is also good. It is particularly important to see that whatever preparation is used is well applied to the *edges*, and rubbed in—the most vigorous fungi are at the edges. A dermatologic friend, in whom I have great confidence, told me not long ago that treatment with 3 per cent sulfur ointment was the best there is and that he had given up the use of gentian violet. He is very likely right, but being a pediatrician and familiar with young babies, I should be a bit shy of using a sulfur ointment as strong as this on them.

Some cases of cutaneous moniliasis apparently arise from an overgrowth of *C. albicans* in the bowel. For this reason it is desirable to give these patients a diet low in carbohydrate, in order to discourage growth of the fungi in the bowel. This was told me a good many years ago by Dr. Rhoda Benham of New York, in whose mycology laboratory I once spent a very profitable morning.

(*To be continued.*)

Too Make oyntment for Scald Heads

Take slices of bacon and fry them then take the greece and set it over the fire, put to it this powder following, take the uper Lether of an old shew, burn it beat it and serce it very fine take the uper shell of an oyster burn it and searce it very fine, take of each of these alike ½ as much brimstone in powder mingle them together and boyle it a while in bacon grece, then put it in the pot for youre use and anoynt the head twice a day.

FROM WILLIAM PENN'S "BOOK OF PHYSICK."

Psychologic Aspects of Pediatrics

THE TREATMENT OF BEHAVIOR DISORDERS IN CHILDREN WITH TOLSEROL

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UNTIL recently, the clinical investigation of drugs in the treatment of psychiatric childhood disorders has received inadequate attention. In an earlier paper[1] the available data were reviewed, and our preliminary observations with Benadryl were reported. The screening procedure to quickly evaluate the possible efficacy of other compounds has continued. This paper is the result of preliminary observation with Elixir Tolserol* (α,β,dihydroxy-γ(2-methyl-phenoxy) propane).

Tolserol was first introduced as a muscle-relaxing agent.[2] It was said to produce a specific depressing effect at the internuncial cell.[3] Other reports further described effective activity on subcortical efferent pathways, basal ganglia, thalamus, hypothalamus, and brain stem.[4] Several investigators[3, 5] noted a sedative effect, and in psychiatric patients Tolserol was said[4, 6] to be effective in relieving anxiety tension states. Finally, it has been used[8] to reduce tension during psychologic testing. Unfortunately, the enthusiasm of many of these investigators is not equally shared by all. The ability of Tolserol to relieve anxiety has been particularly questioned.[9, 10] The use of Tolserol for children has been reported in the therapy of cerebral palsy,[11] but the emphasis in this study was on the control of motor difficulties rather than on behavior.

PROCEDURE

The procedure was essentially as reported in the Benadryl study. There were twenty-two children. Eight were diagnosed as schizophrenia, five organic,* and nine as primary behavior disorders. All the children were chosen at random at the time of their hospital admission, and all were between 6 and 12 years of age. As before, each child was under continuous observation of the staff, i.e., house staff psychiatrist, research staff psychiatrist, nurses, schoolteachers, recreation instructors, and psychologists. During the period of administration of Tolserol, additional compounds were being evaluated in other children on the ward. To exclude subjective opinions and trends as far as possible, the staff was not informed as to the nature of the compound being administered to any child.

Changes were recorded for the following categories:

1. Excessive motor activity.
2. Anxiety.

From the New York University–Bellevue Medical Center, Department of Psychiatry and Psychiatric Division of Bellevue Hospital.

*Supplied through the courtesy of E. R. Squibb & Sons.

*For a description of what is meant by an organic child, see Bender, L.: The Psychological Problems of Children With Organic Brain Disorders, Am. J. Orthopsychiat. 19: 404, 1949.

3. Relationship problems with other children.

4. Relationship problems with adults.

5. Soft neurological signs.

6. Affect.

7. Pathognomic symptomatology and fantasy life, i.e., introjected bodies and hallucinations.

The five-point scale of scoring previously noted was also employed:

++ Marked improvement.
+ Moderate improvement.
0 None or slight change.
− Moderate aggravation.
−− Marked aggravation.

The dosage schedule of the Elixir Tolserol is as follows:

First week: 500 mg. twice a day.
Second week: 500 mg. three times a day.
Third week: 1,000 mg. three times a day.
Fourth week: 1,500 mg. three times a day.

RESULTS

Results are indicated in Tables I, II, and III.* As can be seen in Table I, half of the twenty-two cases showed some over-all improvement; nine were unimproved, and in two there was aggravation of symptoms. The most marked improvement was observed in relationships, both to peer and adults. Nine demonstrated a decrease in manifest anxiety. Only seven of the twenty-two children showed an alleviation of their depression, and six a reduction of hyperactivity. None of the children showed significant change in soft neurological signs, pathognomonic symptomatology, or fantasy life. Ten of the eleven children who showed improvement demonstrated the change in three to five categories, while only one child demonstrated improvement in only one or two categories.

*Statistical analysis was done by Mr. William Helme.

In Table II the data are presented according to diagnosis and age groups. It can be seen that all of the organic children showed improvement with Tolserol. However, there was improvement in only three of eight schizophrenic children, and three of nine children with the diagnosis of primary behavior disorders. Except for the behavior disorders, age did not seem to be a significant factor. Of the four children diagnosed as behavior disorders above the age of 10 years, none showed improvement, while three of the five children between 6 and 9 years showed improvement.

Table III is a breakdown according to intelligence quotient and diagnosis. It would appear from the data that schizophrenic children with IQ's over 78, and children with behavior disorders and IQ's under 78 showed somewhat better response.

DISCUSSION

This preliminary study indicates that Elixir Tolserol is useful in the therapy of children with behavior disorders resulting from organic brain disease. It is less satisfactory in the therapy of children with schizophrenia or primary behavior disorders. In fact, in the latter two diagnostic categories the results are unimpressive. The Elixir Tolserol tended to manifest its effect primarily in improving interpersonal relationships. It was less effective in reducing manifest anxiety.

It is of interest to briefly compare the results obtained with Elixir Tolserol and those reported with Elixir Benadryl. The administration of Tolserol produced the most striking results in children with organic behavior disorders, whereas in those children who received Elixir Benadryl

TABLE I. NUMBER OF CASES IN EACH CATEGORY SHOWING IMPROVEMENT WITH TREATMENT BY TOLSEROL

	IMPROVED	NORMALITY MAINTAINED	UNIMPROVED	WORSE
Hyperactivity	6	1	14	1
Manifest anxiety	9	0	12	1
Relationship problems to peers	11	0	9	2
Relationship problems to adults	10	0	11	1
Depressed affect	7	0	14	1

	IMPROVED	WORSE
Three to five categories	10	1
One to two categories	1	1
No categories	9	0

	IMPROVED	UNIMPROVED	SOME WORSE
All cases	11	9	2

TABLE II

NUMBER OF CHILDREN IMPROVED WITH TOLSEROL TREATMENT BY AGE AND DIAGNOSIS

	AGED 6-9 YEARS			AGED 10-12 YEARS		
DIAGNOSIS	CASES	IMPROVED	NOT IMPROVED	CASES	IMPROVED	NOT IMPROVED
Schizophrenic	4	1	3	4	2	2
Organic	2	2	0	3	3	0
Primary behavior disorders	5	3	2	4	0	4

MEAN NUMBER OF IMPROVED CATEGORIES WITH TOLSEROL TREATMENT

	AGED 6-9 YEARS		AGED 10-12 YEARS	
DIAGNOSIS	CASES	MEAN IMPROVEMENT	CASES	MEAN IMPROVEMENT
Schizophrenic	4	.75	4	.50
Organic	2	3.00	3	4.67
Primary behavior disorders	5	2.40	4	.00

NUMBER IMPROVED AND MEAN IMPROVEMENT WITH TOLSEROL TREATMENT DIAGNOSTIC GROUPINGS ALONE

DIAGNOSIS	CASES	NUMBER IMPROVED	MEAN IMPROVEMENT
Schizophrenic	8	3	.62
Organic	5	5	4.00
Primary behavior disorders	9	3	1.33

TABLE III

NUMBER OF CASES IMPROVED WITH TOLSEROL TREATMENT BY I.Q. AND DIAGNOSIS

	I.Q. UNDER 78			I.Q. 78 AND OVER		
DIAGNOSIS	CASES	IMPROVED	NOT IMPROVED	CASES	IMPROVED	NOT IMPROVED
Schizophrenic	4	1	3	4	2	2
Organic	2	2	0	3	3	0
Primary behavior disorders	4	2	2	5	1	4

MEAN NUMBER OF IMPROVED CATEGORIES WITH TOLSEROL TREATMENT

	I.Q. UNDER 78		I.Q. 78 AND OVER	
DIAGNOSIS	CASES	MEAN IMPROVEMENT	CASES	MEAN IMPROVEMENT
Schizophrenic	4	.25	4	1.50
Organic	2	4.50	3	3.67
Primary behavior disorders	4	2.25	5	.60

there was improvement in all children diagnosed as primary behavior disorders. More detailed analysis of other differences will be postponed until present investigations are completed, and all drugs under study can be compared with each other and with controls.

No toxic symptoms were evidenced in any of the children with Elixir Tolserol. Many children complained of its unpleasant taste. Recent experience with a new related compound, Tolseram, indicates that it has the same therapeutic effect, but is more palatable.

SUMMARY

1. Elixir Tolserol has been administered to twenty-two children with a variety of psychiatric disorders.

2. Administration of this drug produced definite improvement in all the children with the diagnosis of organic behavior disorder.

3. The improvement in children with schizophrenia or primary behavior disorder was unimpressive.

4. The principal improvement was in the area of relationships.

5. Diminution in anxiety was noted in nine of twenty-two children.

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Pediatric Profiles

Oscar Menderson Schloss

(1882–1952)

Oscar in his garden.

OSCAR M. SCHLOSS was born in Cincinnati, Ohio, on June 4, 1882, and died in Southold, New York, on October 13, 1952. He received his undergraduate training at the Alabama Polytechnic Institute (Auburn) and graduated from the Johns Hopkins University School of Medicine in 1905. His hospital training consisted of two years of internship at the King's County Hospital in Brooklyn and a year on the house staff of the New York Nursery and Child's Hospital.

From 1908 to 1922, he managed a busy career in New York encompassing pediatric practice, teaching at Bellevue Medical College, at Columbia with Holt, Sr., and at Cornell, and research in a number of institutions which opened their doors to him: Bellevue Hospital, New York Nursery and Child's Hospital, the Department of Biological Chemistry of Columbia, the Department of Pathology of St. Luke's Hospital. In 1919 he was appointed professor and head of the department of pediatrics at Cornell and pediatrician-in-chief at the New York Nursery and Child's Hospital. In 1922 he went to Harvard as professor of pediatrics and as physician-in-chief at the Infants' and Children's Hospital of Boston, but after two years of frustrating inconveniences, he returned to New York to resume his posts at Cornell.

During the ensuing years, he was one of the planners of the New York Hospital-Cornell Medical College Association, a complex program which required not only the merging of these two institutions but also the affiliations with the New York Lying-In Hospital, the New York Nursery and Child's Hospital, and the Manhattan Maternity Hospital. Respect for his integrity, both by professional and lay members of the various boards in-

From the Departments of Pediatrics of Sinai Hospital of Baltimore and the Johns Hopkins Medical Institutions.

volved, was one of the cornerstones in the founding of a great and expanding institution. From 1927 to 1932, he participated in the detailed planning of the Children's Clinic of the New York Hospital, being aided particularly by the late Dr. Lynne Hoag, beloved associate professor of pediatrics at Cornell, Dr. Samuel Z. Levine, now professor of pediatrics at Cornell, and Dr. Vernon W. Lippard, then chief resident in pediatrics at Nursery and Child's, now Dean of the Yale School of Medicine. In September, 1932, he assumed the professorship at Cornell on a full-time basis and pointed the department along the productive road it has traveled under Dr. Levine's leadership since 1934. He was a much-sought advisor by other clinical department heads, faced as some were not only by the strangeness of a new city and a new institution, but also by the anxieties, free-floating or specific, of various members of their staffs who feared full-time for personal reasons of varying validity. His own previous experience as private practitioner, as part-time professor in New York and as full-time professor in Boston made him a particularly tolerant counselor, not likely to think that all the right was on either side of the problem. In the pediatric department, of course, respect for the different skills of men of varied past experience was a natural outgrowth of the professor's own background. This was witnessed by the fact that when the department of pediatrics of Cornell was transferred from Nursery and Child's to the New York Hospital, and full-time became the ruling principle, adequate laboratory space and support were supplied for Dr. Carl Smith who has continued over the years to contribute to pediatric hematology while engaging in an active pediatric practice.

It was ironic that administrative difficulties which beset the new hospital because of the financial depression turned the position which he had assumed with such high hopes into one which in 1934 he felt compelled to leave to return to private practice. Some of his thinking in the matter will be discussed later.

From 1934 until 1948 he continued as attending pediatrician at the New York Hospital and professor of clinical pediatrics. He made ward rounds twice weekly for most of the academic year, and alternated with Dr. Levine in conducting weekly grand rounds. In 1948 he became professor emeritus and consulting pediatrician, and until his death he continued to serve as clinician, teacher, and personal advisor.

Now what manner of man was this who called forth from his patients such deep devotion, from his colleagues and students such deep respect? Because he was essentially a shy person, he was not easy to know and I will not attempt a comprehensive personal characterization. Because it was my good fortune first as undergraduate student, and later as house officer and member of the full-time staff at Cornell, to have this great physician as teacher, standard bearer, and personal counselor, the following paragraphs may supply some parts of the picture.

First, I wish to write of his research career. From 1908 when he completed his house staff training until 1922 when he went to Harvard, he published some forty-four papers. Their range portrayed the clinical in-

vestigator at his best, taking questions from the bedside to the laboratory for study and bringing back to the patient direct and indirect benefits either from the results, both positive or negative, or from the critical methodology used in the laboratory. An interest in "The association of rheumatic fever and the erythema group of skin diseases" (Am. J. M. Sc. 140: 226, 1910) led to "The injection of rhesus monkeys with blood from patients with rheumatic fever" (J. A. M. A. 59: 1946, 1912) and to studies with another master clinician, Nellis B. Foster, of "Experimental streptococcal arthritis in monkeys" (J. Med. Research 29: 9, 1913). Interest in the eosinophilia of helminthiasis (Am. J. M. Sc. 139: 675, 1910) led him to studies of "The normal percentages of the different varieties of leucocytes in infants and children" (Arch. Int. Med. 6: 638, 1910).

His interest in problems of the newborn infant was reflected in the first of his papers on metabolism, with J. L. Crawford: "The metabolism of nitrogen, phosphorus and the purine substances in the newborn; with special reference to the causation of uric acid infarcts of the kidney" (Am. J. Dis. Child. 1: 203, 1911). In this same initial volume appeared the excellent survey with L. J. J. Commiskey of the etiology and treatment of "Spontaneous hemorrhage of the newborn." Although "the curative effect of blood transfusion was immediate," the subcutaneous injections of whole blood were recommended because "the technical difficulties of transfusion in a young infant are formidable and render the method available only in the hands of a very skillful surgeon." In later years when pediatric interns had replaced the "skillful surgeon," they found that the cross-matching of blood before transfusion was always their responsibility, never to be sloughed to a technician.

In 1912 came one of his two greatest contributions to modern medicine, his report "A case of allergy to common foods" (Am. J. Dis. Child. 3: 361, 1912). Under this simple title, he reported an 8-year-old boy who developed urticaria on ingestion of eggs, almonds, and oatmeal. From the discussion of his paper presented at the New York Academy of Medicine, it is obvious that clinicians knew of specific food poisonings or idiosynerasies. Dr. Schloss, aware of the concepts developed by Von Pirquet and Schick on tuberculin allergy, demonstrated that cutaneous inoculation of these foodstuffs produced an immediate urticarial wheal at the site of inoculation. Furthermore, the reactions were produced only by the protein constituents which he extracted from these foods. Guinea pigs were sensitized to ovomucoid, one of the proteins of egg, by intraperitoneal injections of the patient's blood serum, and it was shown that feeding ovomucoid in gradually increasing doses immunized or desensitized the patient. At the same time, an immunity to oatmeal and an apparently decreasing susceptibility to almonds occurred. Although H. L. Smith (Arch. Int. Med. 3: 350, 1909) reported at approximately the same time local and general reactions to cutaneous application of buckwheat in "A case of buckwheat poisoning"—the experiments were performed with Drs. Wm. Thayer and Rufus Cole in Dr. Cole's office—it is fair to say

that Dr. Schloss' elegant experiments supplied the basis for the use of skin testing with allergens as a diagnostic measure in medical practice. It was a measure of objectivity toward his own brain child that in his teaching of house officers he repeatedly called to our attention the limitations of determination of skin hypersensitivity as a guide to hypersensitivity of the tissues in which symptoms arose. These limitations were mentioned in his first papers. The importance of false positives and negatives, the need to determine by careful history without skin testing what allergens warranted further investigation, the final judgment from the clinical trial were part and parcel of his everyday teaching. Needless to say, the uninformed among us were surprised to hear from Dr. William Schmidt who continued some of the studies at New York Hospital begun by Dr. Schloss that the skin testing of which he was so critical had been derived from his own basic observations made over the period from 1912 to 1936 with Drs. T. W. Worthen, Arthur F. Anderson, Robert O. DuBois, Harold C. Stuart, and Vernon Lippard.

During these same fruitful years came his outstanding contributions to our modern knowledge of the physiologic imbalance in infants with diarrheal disorders. The importance of acidosis was described in papers with Dr. Rufus Stetson on "The occurrence of acidosis with severe diarrhea" (Am. J. Dis. Child. 13: 218, 1917) and with Dr. Helen Harrington: "Comparison of the carbon dioxide tension of the alveolar air and the hydrogen ion concentration of the urine with the bicarbonate of the blood plasma" (Am. J. Dis. Child. 17: 85, 1919). Dr. E. A. Park has already written how Dr. Schloss, hearing that Howland and Marriott had made independent studies with similar results, withheld his publication until theirs had appeared. When this item was mentioned to Dr. Schloss after it had been turned up by chance in a memorial address given by Dr. Park for Dr. Marriott, Dr. Schloss brushed it aside, his recollection being chiefly of the excitement of the phone calls to Baltimore.

In one of his most elegant papers, "Intestinal intoxication in infants; the importance of impaired renal function" (Am. J. Dis. Child. 15: 165, 1918), he not only gave us a basis for understanding the source of some of the disorders in these infants, but he also taught us to think dynamically of infants with disease. This was best summed up in the statement to house officers who became too precise in their calculations of fluid repair therapy: "The trouble may lie in the fact that we are dealing with a funnel rather than a test tube." A common interest in kidney function provided one basis for the enduring intellectual and emotional ties between Dr. Schloss and Dr. James Gamble, Sr., who joined the department of pediatrics of Harvard at Dr. Schloss' invitation.

The breadth of his interests is indicated by the subjects of his last papers: "Non-diabetic ketosis in children" (with C. A. Weymuller, Am. J. Dis. Child. 34: 549, 1927), "Pathology of so-called acute pyelitis in infants" (with J. R. Wilson, Am. J. Dis. Child. 38: 227, 1929), "Interpretation of some recent advances in medicine in terms of equilibrium" (Presidential address, American Pediatric Society, Am. J. Dis. Child. 46:

1, 1933), and "Immune reactions induced in infants by intestinal absorption of incompletely digested cows' milk protein" (with Vernon W. Lippard and P. A. Johnson, Am. J. Dis. Child. 51: 562, 1936).

As one reviews his scientific contributions one is impressed with the catholicity of his clinical and laboratory interests, the clarity of his thinking, the simplicity of his approaches and writing, his objectivity toward his own work, his great modesty. One can easily understand why Dr. Park recently stated that his loss to full-time academic pediatrics was a tragedy for American medicine. It is difficult to conceive how he could have been so productive scientifically during the early years when his livelihood depended entirely on the pediatric practice he was building. When this question was recently broached to Mrs. Schloss she gave part of the answer: "When he had an idea, it drove him." With Mrs. Schloss serving coffee, he worked far into the night in limited laboratory space provided at one time by Dr. A. Gettler, toxicologist at Bellevue Hospital. Mrs. Schloss is quite convinced of the efficacy of caffeine for she noted promptly the effects of substitution of Sanka. It becomes quickly obvious, too, that Mrs. Schloss served as an important helpmate, sharing actively his deep interest in sick infants and children. Her initial interest in the young man had been quickened by his kindliness to the parents of sick infants for whom he was responsible in the outpatient department of Bellevue Hospital—as a nurse in the same department she had ample opportunity to observe him in action.

The burning nature of the curiosity which led to such a productive research career may partly explain the low tolerance for frustration which led him to resign the full-time professorships at Harvard in 1924 and at Cornell in 1934. The reason he mentioned for his departure from Harvard was lethargy on the part of the administration in meeting what had been considered firm commitments during pre-employment negotiations. Apparently a time limit was set by Dr. Schloss for clarification of misunderstandings, but this was not met, and he decided to return to the professorship at Cornell, filled by Dr. Louis Schroeder on an acting basis, a few days before the necessary steps were taken at Harvard. This experience left him with an abiding distrust of diplomatic administrators who say yes when they mean maybe, and maybe when they mean no. I have been told that the coolness of Boston pediatricians in accepting him as a pediatric consultant, a matter of practical importance, was one of the considerations which led to his decision to resign. This experience may also have contributed to his disinclination to consider another important pediatric post which would have required his leaving New York.

I am more directly familiar with the circumstances that surrounded his resignation from the full-time professorship at Cornell. As already stated he had spent many hours in planning and dreaming not only for the New York Hospital-Cornell Medical College Association but also for its Children's Clinic with its two floors of outpatient department facilities, its four floors of inpatient pavilions, its air-conditioned nurseries

for premature infants, its play-roof, its sub-sub-basement with air-conditioned laboratories for metabolic research, and its crowning floor of laboratories for other investigative work. Next to his secretary's office was a laboratory in which he had expected to return to direct participation in investigative work. His high hopes for a more scholarly existence were soon thwarted.

As one looks back and pushes personalities aside, two factors emerge as of major importance. One was the financial depression. Ground had been broken for the new medical center just before the stock market crash in 1929, and the edifice was built according to previous plans on the then all too common assumption that prosperity was just around the corner. An operating budget for the New York Hospital was set up for the months of September to December, 1932, but in spite of adherence to it, it became apparent—perhaps the results of the national election convinced the few remaining optimists—that the new center was in for a hard pull. This took the form of items ranging from cessation of free distribution of milk by the hospital social service to indigent pediatric outpatients to unscheduled visits from a board member to the professor to complain of the waste arising from deposit of soiled diapers in the garbage chute. Ability to maintain the budget for support of a good full-time department also became a matter of serious question. Dr. Schloss knew from personal experience the problems entailed in making one's own way financially from practice while trying to do research; he felt strongly that the young investigator and his family ought to be given sufficient security so that he would not be distracted during his most productive years. He believed that once a man had developed a sufficient reputation he could probably earn part of his livelihood from a limited consultation practice. Although the New York Hospital-Cornell Association had committed itself to a strict full-time system similar to that at Hopkins, Dr. Schloss urged the administration to permit him privileges such as now exist in many institutions with modified or geographic full-time arrangements. When this suggestion was rejected he asked to have all pediatric fees earmarked for the budget of the department of pediatrics rather than for the budget of the hospital as a whole. For reasons which now seem inadequate as one sees various successful modifications of strict full time, no compromise was offered by the administration, and in the depressing days of 1932 to 1934—Dr. Schloss had little faith in the New Deal—he was pessimistic about his ability to meet commitments he had assumed during his years as a successful, albeit very simply living, practitioner in New York. The fatal illness of Dr. Hoag was an added source of emotional turmoil.

I believe, however, that there was another very personal reason for his sense of frustration, one which has to be faced regularly by men who become heads of clinical departments, with the load of both medical school and hospital responsibilities.

Men whose satisfactions as physicians, teachers, or investigators have been based at least partly on their sense of intimacy with patients, students, or research problems are pro-

moted to positions with great administrative responsibilities. Some are sufficiently well organized to compartmentalize their activities; others recognize the limitations of their new positions and give up active participation in those parts of their job which require personal attention—they make these adjustments with varying degrees of ambivalence. But Dr. Schloss was not such a person. "When he had an idea, it drove him," Mrs. Schloss has said, and the devotion and respect of his patients was at least partly the reflection of his own devotion to them as individuals. Although it is true that his first years at New York Hospital-Cornell were made more difficult by the depression, yet one must consider that any administrative job of the size of the directorship of a clinical department in a large medical center would have run against his grain.

The simplicity and unpretentiousness of his way of life, both personal and professional, made him a natural enemy of what Brandeis has termed the "curse of bigness." He probably sensed early that the "managerial revolution" which Burnham has described for big industry would constitute a problem for big medicine as well. The development of big medical centers has stemmed partly from specialization within medicine, but partly it has reflected the drive toward bigness in our country as a whole. Its rate of development has been speeded up by the war effort and the continued large support for research. How shall one resolve the dilemma for the teacher of medicine who, on the one hand, derives satisfaction from personal contacts with patients and students, and at the same time recognizes his administrative responsibilities, which seem to increase geometrically as institutions grow bigger. Perhaps those interested in operational analysis as well as in the personal problems of the scientist would find this a profitable field for research.

So much for these considerations which contributed to his decision to give up full-time and return to the continuing career as great teacher and physician at Cornell. What were some of his characteristics as a teacher? The most outstanding one was his scholarliness. At regular ward rounds, interesting patients were presented, with all information available to the time of presentation, and not as subjects for diagnostic guessing games—this was to him wholly unrealistic even though it might serve admirably to sharpen wits. From the wealth of his clinical experience, from his broad knowledge of the literature, from his experience as an investigator, would then come both a balanced and critical analysis and this the first time the patient was presented. For the weekly clinical conference, attended by many outside physicians, patients were chosen, however, at least three days prior to presentation. This permitted Dr. Schloss to review the most recent literature and a polished, complete analysis of two, three, or rarely four patients was our reward every Friday afternoon at four. Exciting cases might be admitted on the night before the conference; these were regularly presented to him at ward rounds, but never for exhibition of his fine clinical acumen before a large audience. The concept of intuitive diagnosis was foreign to his sense of logic—he once said that his private

patients could be divided into two groups: those who believed that diagnoses were arrived at by simple addition of systematically collected facts, and those who wanted an intuitive, semimystical approach. Over the years his refusal to offer the latter served as a built-in screening device which permitted him to order his life so that he could devote time to teaching and to reading and to quiet vacations at Southold, where he indulged his love for flowers and photography.

His teaching clinics for students consisted of an initial demonstration of a patient, whose salient features were described to the class by one of the students chosen by the chief resident to sit in the front row. After gentle questioning of the student by the professor came a systematic presentation of facts about the disease just illustrated. I remember the time I was called from the front row by Dr. L. Weymuller, then chief resident, to describe to the other third-year students crowded into a small classroom at Nursery and Child's a newborn infant with numerous ecchymotic areas in the skin. When asked for a diagnosis, I suggested "purpura hemorrhagica neonatorum," to be told gently, "Yes, but we call it hemorrhagic disease of the newborn." His own presentations were direct, simple, concise, and in flawless English; when he was under tension his fluency was interrupted by a certain amount of stammering. At one time he had stammered a good deal, and the apparently effortless delivery with which we were familiar was the result of much practice reciting poetry aloud.

The most important part of his teaching was, of course, not in these formal lectures or clinics but rather in the example he set: gentleness toward all patients and parents, whether from slum or mansion; a sternly critical attitude in the study of disease; high standards of excellence; scholarliness; a refusal to confuse shadow with substance. (Academic rank was "tail feathers.") How can I characterize what was taught when as an assistant resident I first brought to him a plan for studying the metabolism of premature infants. He asked me if I realized that I might obtain no practical results for ten years. When I responded, naively indeed, that this had not appeared of any particular concern, his answer was a simple "God bless you then."

Most of what needs to be said to characterize Dr. Schloss as physician to sick children and their worried parents has already been said. His remarkable intellectual powers and broad experience permitted him to give to his patients the best that medicine had to offer; and for this his patients respected him. But the love and devotion came not only from the benefits of his technical skills, but even more from his unfailing gentleness and courtesy. This did not mean that he permitted unreasonable people to run him ragged, rather he defined his responsibilities. This was done partly by limitation of the size and location of his practice; it was jokingly stated that he could make most of his house calls on foot, walking from one apartment house to another in midtown Manhattan. Consultations outside this area were usually made only to help former house officers. Telephone calls were sharply circumscribed by devoted secretaries who bore the onus of protecting him.

Once when I called for an appointment at his request, I was finally given one for 4:45 P.M., with the clear implication that I could have only fifteen minutes.

A self-selecting process weeded out parents who were not satisfied with his limited availability; he encouraged parents to have faith in their own judgment about minor complaints, remembering that children recovered spontaneously from most febrile illnesses. This, as well as his natural skepticism, was responsible for the caution with which he used sulfonamides in nonhospitalized patients. On one occasion a house officer asked him what he thought of the use of bismuth for the treatment of diarrhea. He said he used it occasionally for private patients, but never for ward patients, and guessed therefore it was not of proved benefit. His attitude was similarly skeptical toward the changing formulations of child psychiatry, particularly during the early thirties when communications between pediatrics and psychiatry left so much to be desired.

Although he limited sharply the size of his practice, there was, of course, no limitation in his feeling of responsibility to those patients who were willing to permit him a reasonable ordering of his own life. Parents who waxed enthusiastic about him as pediatrician were grateful not only for his technical skill, but for his gentleness, his calm, his willingness to respect their intelligence.

After his retirement to Southold, families drove almost the whole length of Long Island for checkups, and neighboring physicians brought their difficult problems for consultation. In his simple home on the bay, he read and gardened and had time for photography. Mrs. Schloss tells that he took care of his roses and peonies just as he took care of babies—his conscience would permit no neglect of his flower beds, and the house was full of flowers all year round. Here he died peacefully in his sleep—immortal not only in the memories of his family, but also in the children whom he had healed, the parents whose anxieties he had assuaged, the hospital and medical school to whose development he had contributed so much, the students and colleagues for whom he had set such high personal standards as physician, teacher, investigator.

Harry H. Gordon

Comments on Current Literature

PLATELET GROUPS AND TYPES

EARLY observations[1, 2] that the administration of heterologous platelets to animals stimulates the production of specific antiplatelet "immune" serum, which, when injected into the circulation of the donor animals, results in marked thrombocytopenia, have been extended and verified. As has been summarized in a number of review articles, evidence for platelet iso- and autoantigenicity has accumulated from clinical and laboratory studies of the thrombocytopenic purpuras, and in the course of platelet transfusion studies, as well as from the experimental study of reactions following the injection of such modified plasma into normal recipients.[2, 3]

The continued observation that platelets are antigenic suggested the existence of individual platelet groups and types comparable to the red cell groups, eight individual types being postulated originally. Within the past eighteen months to two years, several extensive investigations[2, 3] have been reported which focus attention upon the clinical importance of the platelets and their specificity, implying "the use of only compatible platelets for transfusions on the same lines as for whole blood."[4]

In 1953 Stefanini, Dameshek, and their co-workers[2] presented strong evidence for the antigenicity of platelets from observations obtained in the course of platelet transfusion studies. Patients with secondary, or *amegakaryocytic,* thrombocytopenic purpura show progressively less benefit from repeated platelet transfusions, the survival time of the transfused platelets being progressively shortened. At the same time these patients may develop iso- and, occasionally, autoplatelet agglutinins, and their plasma may induce thrombocytopenia when injected into (normal) recipients who are v u l n e r a b l e. Development of platelet agglutinins o c c u r s more promptly when *viable,* well-preserved platelets are used for transfusion. By direct cross-testing techniques Stefanini and his group were able to detect naturally occurring platelet agglutinins in human subjects, suggesting the existence of four basic platelet groups: I, II, III (I + II), and IV (0 group : no antigen). The incidence reported by these authors was based on evidence obtained from a total of 285 individuals tested. Agglutinin absorption tests and in vivo immunization tests have confirmed the presence of such groups. They are not related to the ABO antigenic system of the red blood cells, but since they can be detected by the use of naturally occurring agglutinins, are considered to have an antigenic significance similar to that of the ABO antigenic system.

Occasional patients receiving multiple transfusions develop agglutinins against their own platelets (autoagglutinins) as well as isoagglutinins, and become thrombocytopenic as a result. These authors[2] have suggested that "some such mechanism with the development of platelet auto-sensitization, may result in idiopathic thrombocytopenia." In some instances of idiopathic thrombocytopenia, a platelet autoagglutinin can be detected. In a series of nine patients reported, the agglutinin disappeared in five of the nine following successful splenectomy, although the platelet isoagglutinin, also present, persisted

after the surgery. "This finding may indicate that autoimmune thrombocytopenia is improved by splenectomy, even if isoagglutinin production continues, and suggests an additional possible mechanism to explain the favorable effect of splenectomy in many cases of the disease."[2]

In a summary of nine cases of thrombocytopenia and thrombopathia treated by means of repeated platelet transfusions, Van Creveld and his associates[3] (1953) stress the fact that they employed for such transfusion only blood of the same ABO and Rh groups, since the antigenic potentialities of the thrombocytes were not known to them. In all nine patients, a steady increase in the number of platelets was observed, and the patients showed benefit from the repeated platelet transfusions.

Somewhat more recently investigations by Gurevitch and Nelken[4] have verified the four blood-group classification of platelets, corresponding to the ABO groups of erythrocytes; these authors describe in some detail the preparation of the specimen and the procedure of typing the platelet suspension. Control examinations of platelets were carried on simultaneously, the "control" thrombocytes being suspended in their own serum or in inactivated serum of the same group. Gurevitch and Nelken examined for their antigenic behavior eighty-five different samples of platelet suspensions, and in every instance the results showed exact correspondence between the erythrocyte and the thrombocyte groups. The identity of the A and B antigens in platelets and in red blood cells was verified by adsorption of isoagglutinins by erythrocytes and thrombocytes, by the inhibition of isoagglutinins with saliva, and the neutralization of sera by group-specific substances. Storage of platelet suspensions in the refrigerator up to seven days resulted in gradual loss of agglutinability by antisera.

A recent preliminary publication in the *Journal of Laboratory and Clinical Medicine*[6] (May, 1955) by Nicola, Rosti, and Zangaglia of the University of Pavia, Italy, is of interest in connection with the group classification of thrombocytes and the significance of their antigenic activity. Preliminary results described by these investigators indicate that, as might be expected from theoretical implications, platelet antibodies can be detected by means of a complement fixation test. The findings are based on studies of antiplatelet rabbit sera and guinea pig platelets. Complete inhibition of hemolysis took place at the serum dilution of 1:700; no inhibition of hemolysis was observed with serum specimens obtained from the same animals prior to immunization. This investigative lead is being pursued at present, especially with reference to possible correlations with human pathology.

Such observations as these on platelet immunology have confirmed the heteroantigenicity of the thrombocytes, and have raised questions as to the significance of their iso- and autoantigenicity, not only in connection with patients having idiopathic thrombocytopenic purpura, and in relation to repeated platelet transfusion, but also in connection with the possibility that autoagglutinins might develop "in response to antigenic stimulation by platelet products or platelets damaged by various agents (viruses, etc.)."[2] Further developments in this field concerning the antigenic behavior of the thrombocytes will be of considerable interest.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

A warning needs to be given pediatricians and obstetricians about using unduly large doses of any water-soluble vitamin K preparation in premature infants. Communications appearing in the *Lancet*[1, 2] report fatal hemolytic anemia occurring in two small series of infants. The vitamin K was given in one or more doses of 10 mg. to these premature infants. No evidence of blood group incompatibility or Rh factor problem was found.

A further report appeared[3] in substantiation of the hemolytic effect of very large doses (100 mg. per kilogram) of water-soluble vitamin K given to rats. This hemolysis occurred only in rats deprived of vitamin E. It is known[4] that vitamin E deficiency in rats leads to abnormally great hemolytic tendency. Recent work, as yet unpublished, has confirmed this for adult human beings. It has been reported[5] that the human fetus and infant tend to have small amounts of vitamin E in tissues.

The dose of vitamin K, which is adequate when given antepartum for prevention of hemorrhagic disease in the newborn, is usually thought to be 1 mg. Parenteral administration of 5 mg. to infants has had wide use and without hazard being reported, even in premature infants.[2] Too frequently, physicians have assumed that great overdosage of vitamins is innocuous. This is unwise, especially so far as parenteral administration of thiamine or niacin is concerned. The recent reports draw attention to upper limits for water-soluble vitamin K, at least in premature infants. There is no reason to fear harm from the long-established dosage range up to 5 mg. Neither is there any reason to use a much larger dosage. No unfavorable reports have appeared concerning oral use of the water-soluble vitamin K.

ELMER L. SEVERINGHAUS, M.D.

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4. Rose, C. S., and György, P.: Blood **5**: 1062, 1950.
5. Dju, M. Y., Mason, K. E., and Filer, L. J., Jr.: Etudes neo-nataies **1**: 49, 1952.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at New York City, June 10, 11, and 12, 1955.

Dr. Donald K. Adler, 863 Central Ave., Woodmere, L. I., N. Y.

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Dr. Harriet Mitchell Arey, 215 Avon Rd., Narberth, Pa.

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Dr. Morton Mitchell Axler, U. S. Army Hospital, Fort Eustis, Va.

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Dr. Adelaide Frick, 274 Old Short Hills Rd., Short Hills, N. J.
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Dr. Jeanne Marcoux Horan, Tulane University Medical School, New Orleans, La.
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Dr. Bernard D. Zaleznak, 750 St. Marks Ave., Brooklyn 16, N. Y.

The following oral examinations have been scheduled by the Board:
Chicago, Ill., Oct. 7, 8, and 9, 1955.
Washington, D. C., Dec. 2, 3, and 4, 1955.

The **VIII International Congress of Paediatrics** will be held at Copenhagen, July 22 to 27, 1956. The scientific program will comprise plenary sessions, roundtable conferences, sectional meetings, and an exhibition. At the plenary sessions the following lectures will be held:

Monday, July 23: I. *Prenatal Injuries and Malformations.* (1) Genetic injuries from irradiation (atomic bomb). (2) Prenatal infections. (3) Prenatal prophylaxis. II. *Chemical Agents.* (1) Fluoridated water in the prevention of dental caries. (2) Dangers involved in the use of antibiotics. (3) Dangers from industrially manufactured foods.

Tuesday, July 24: I. *Pathology of the Newborn*: *Anoxia.* (1) Mechanism of anoxia. (2) Pathological anatomy of anoxia. (3) Oxygen therapy—value and risks. II. *Surgery.* (1) Malignant diseases in childhood. (2) Urological problems. (3) Late results of operation for cyanotic heart diseases.

Wednesday, July 25: I. *Child Psychiatry.* (1) Neuroses in childhood. (2) Prevention of accidents. (3) Early diagnosis of mental deficiency. II. *Neurology.* (1) Hydrocephalus. (2) Cerebral palsy—results of long-term physiotherapy. (3) Kernicterus.

Thursday, July 26: I. *Infections*: (1) Vaccination against poliomyelitis. II. *Allergy.* (1) Bacterial allergy: diagnosis and incidence. (2) Bacterial allergy: treatment and results.

Friday, July 27: I. *Problems in Tropical Paediatrics.* (1) Kwashiorkor. (2) Chagas' disease. (3) Ascariasis. II. *Tuberculosis.* (1) Prophylaxis of tuberculosis. (2) Treatment of primary tuberculosis. (3) Treatment of tuberculous meningitis.

Proffered papers will be read in sectional meetings.

It is also planned to arrange roundtable conferences with the following subjects: (1) Auricular septal defect; (2) epilepsy; (3) leukemia; (4) hemophilia; (5) amino acid metabolism; (6) nephrosis; (7) water and electrolyte metabolism in dehydration; (8) the adrenogenital syndrome.

Films of paediatric interest will be shown in the Congress Cinema. A scientific and technical exhibition will be arranged in connection with the Congress. The preliminary program will be sent out in a few weeks. For further information please apply to: VIII International Congress of Paediatrics, Domus Medica, 12 A Kristianiagade, Copenhagen Ø, Denmark.

Those planning to attend the **International Congress of Pediatrics** at Copenhagen next summer may be interested in a correlated **Studytour** which will provide opportunity before or after the sessions to meet some outstanding European pediatricians and to visit a few of the best hospitals in England, Norway, Sweden, Den-

mark, Holland, Germany, Switzerland, and France. Sightseeing and recreation will also be provided in each city abroad and wives and friends are welcome to join the party. Arrangements are being made at cost by World Studytours, a nonprofit educational corporation. Inquiries may be directed to the leader, Ernest S. Watson, M.D., 266 Claremont, Elmhurst, Ill., or to World Studytours, Box 523, Rye, N. Y. If steamship accommodations are desired, reservations need to be made before the end of November, 1955.

At the sixty-fifth annual meeting of the **American Pediatric Society** held in Quebec, June 14, 1955, the following officers were elected for 1955-1956:

President: Dr. Allan M. Butler
Vice President: Dr. Bruce Chown
Secretary-Treasurer: Dr. Aims C. McGuinness
Recorder-Editor: Dr. Stewart H. Clifford

Members of the Council:

For a five-year term: Dr. Charles A. Janeway
For a six-year term: Dr. Edward C. Curnen, Jr.
For a seven-year term: Dr. J. Harry Ebbs

The following were elected to active membership:

Dr. Robert A. Aldrich, Portland, Ore.
Dr. Ogden C. Bruton, Washington, D. C.
Dr. Robert E. Cooke, New Haven, Conn.
Dr. John D. Crawford, Boston, Mass.
Dr. Robert A. Good, Minneapolis, Minn.
Dr. Eugene Kaplan, New Orleans, La.
Dr. Haddow M. Keith, Rochester, Minn.
Dr. Charles U. Lowe, Buffalo, N. Y.
Dr. Frederick C. Robbins, Cleveland, Ohio.
Dr. Warren E. Wheller, Columbus, Ohio.

The following officers were elected for 1955-1956 at the annual meeting of the **Society for Pediatric Research** held at Quebec:

President: Dr. Wolf W. Zuelzer
Vice President: Dr. Nathan Talbot
Secretary-Treasurer: Dr. Sydney S. Gellis

Members of the Council: Drs. Henry Kempe, Charles Lowe, Margaret Smith, Henry Barnett, Fred Robbins, Andrew Chute, and Robert Aldrich.

The annual **Congress of the Italian Association of Pediatrics** will be held in Perugia on Oct. 9, 10, and 11, 1955. It will be organized by Prof. Pio Ritossa, director of the pediatric clinic of the University of Perugia. Prof. Giuseppe Caronia is president of the Congress.

A postgraduate course in Pediatrics for the General Practitioner will be given at the **Hospital for Sick Children,** Ste. Justine, Montreal, Canada. The course of one week's duration will start Monday, September 26, at 9 A.M. Lectures, presentation of cases, and practical demonstrations have been arranged to cover the common disorders of children and preventive pediatrics. The teaching is in French. For further information, write to Dr. Paul Letondal, Committee on Public Relations, Hospital for Sick Children, Ste. Justine, Montreal, Canada.

The **New York Academy of Medicine** will hold its twenty-eighth annual graduate fortnight Oct. 10 to 21, 1955, on Problems of Aging. For a detailed program, write the Secretary at 2 East 103rd St., New York 29, N. Y.

The **University of Minnesota** will present a continuation course in Pediatrics for Pediatricians Sept. 21 and 22, 1955. Presented under the auspices of the Center for Continuation Study, the course will be held in the Mayo Memorial Auditorium on the University Campus. One-half day will be devoted to each of the following general subjects: infectious diseases, hypersensitivity diseases, central nervous system disorders, and endocrine and metabolic abnormalities. The guest faculty will include Dr. Lewis Thomas, professor of pathology, New York University College of Medicine, New York City, who will also deliver the Irvine McQuarrie Lecture on Thursday evening, September 22. The course will be presented under the direction of Dr. John A. Anderson, head of the department of pediatrics. Registrants will also be invited to attend the meeting of the **Northwest Pediatrics Society** which will be held on September 23. Lodging and meal accommodations are available at the Center for Continuation Study.

Book Reviews

Viral and Rickettsial Diseases of the Skin, Eye, and Mucous Membranes of Man. Harvey Blank, M.D., and Geoffrey Rake, M.B., Boston and Toronto, 1955, Little, Brown and Company, 285 pages. Price $8.50.

This volume, described in the publisher's announcement as "the first detailed book on viral and rickettsial diseases that affect primarily the coverings and orifices of the body," is timely and fills a definite need. The illustrations are excellent and numerous, with many in color. In some respects the volume may very well serve as a physician's handbook. The charts and tables are clear cut, summarizing much useful information.

The chapter on the diagnosis of viral and rickettsial infections describes the recognized, commonly employed diagnostic procedures, and includes a list of laboratories in the United States where such procedures are being carried out routinely, some of which are State Health Department Laboratories, or located in Public Health Centers, and some of which are Medical Laboratories connected with U. S. Army areas.

While the chapter bibliographies are excellent so far as individual references are concerned, they cannot be considered complete since much pertinent pediatric literature has been omitted.

Casimir Funk. Benjamin Harrow, New York, 1955, Dodd, Mead & Co., 209 pages. Price $4.00.

An interesting and readable biography of the Polish-born biochemist Casimir Funk, who gave the word "vitamin" to the medical profession and the world. The first part takes the reader through Funk's many wanderings in European countries and the United States: Switzerland, Paris (Pasteur Institute), Berlin, London (Lister Institute), New York, Warsaw, Paris again, and finally New York since 1939. There is obviously a restlessness in the man which is further reflected in his scientific interests.

The author, a well-known chemist who recently retired as head of the department of chemistry at the city college of New York, in the second part discusses Funk's scientific contributions in the fields of vitamins, sex hormones, cancer, insulin, nutrition, and enzymes. Dr. Harrow is unusually equipped for the task he undertook, and has produced as satisfactory a biography as is possible in the discussion of a living person. The reviewer found the book of interest.

Handbook of Pediatrics. H. K. Silver, M.D., C. H. Kempe, M.D., and H. B. Bruyn, M.D., Los Altos, Calif., 1955, Lange Medical Publications, 550 pages. Price $3.00.

This is a small pocket-sized book printed on very thin paper and in small 6 point type. It is intended as a digest for the student and practitioner rather than a replacement of the standard texts. It contains a wealth of material and excellent tables and charts. The material is presented in a clear, concise manner and is up to date. Except for the eyestrain involved, it is a useful, practical synopsis or digest.

Fluoroscopy in Diagnostic Roentgenology. Otto Deutschberger, M.D., Philadelphia, 1955, W. B. Saunders Co., 888 pages. Price $22.00.

In an extensive text, Deutschberger first discusses the techniques, evaluation, and hazards of fluoroscopy. This is followed by a detailed discussion of its clinical use in the diagnosis of conditions of the head, neck, chest, abdomen, and extremities. About one-third of the text considers pulmonary and cardiac lesions. With the increasing use of fluoroscopy in the private office, the practitioner will find it of considerable value in his interpretation of the fluoroscopic image.

The Care and Feeding of Twins. Phyllis Graham, New York, 1955, Harper & Brothers, 242 pages. Price $3.50.

This is an unusual book for parents which the physician might well keep in mind to recommend when he finds himself responsible for the medical care of twins. Mrs. Graham, the mother of identical twins, discusses the many problems that twins create as regard feeding in infancy, clothing, bathing, and the early social and education adjustment. Mrs. Graham stresses the importance of not letting each lose his individuality in the joint relationship that necessarily exists between the two. The weakness in the text is its

failure to differentiate clearly between the problems that occur with identical twins and fraternal twins. The important problems that arise as twins grow older vary markedly between the two types. The book, however, gives useful and practical advice on meeting the many household problems that arise when the twins are young.

Books Received

Therapie der Kinderkrankheiten. Prof. Dr. Josef Siegel, Vienna, 1953, Wilhelm Maudrich Verlag, 432 pages. Price $8.00.

Survey of Clinical Pediatrics, ed. 2. L. B. Slobody, M.D., New York, 1955, McGraw-Hill Book Co., 502 pages. Price $9.50. A second revised edition of Slobody's text which was reviewed in the JOURNAL in 1953.

Better Health for Your Children. I. Newton Kugelmann, M.D., New York, 1955, McGraw-Hill Book Co., 341 pages. Price $4.75. A text for parents.

Ion Exchange and Adsorption Agents in Medicine. Gustav J. Martin, Sc.D., Boston, 1955, Little, Brown and Co., 333 pages. Price $7.50. The concept of intestinal bionomics.

Evaluation in Mental Health. Report of a Subcommittee of the National Advisory Health Council, U. S. Department of Health, Education, and Welfare, Washington, U. S. Government Printing Office, 292 pages. Price $2.00.

Hypertension, Humoral and Neurogenic Factors. Edited by G. E. W. Wolstenholme and Margaret P. Cameron, Boston, 1954, Little, Brown and Co., 294 pages. Price $6.75. Report with over 20 papers on a symposium in 1953 held by the Ciba Foundation in London.

Die Ursachen der Kinderlähmung und verwandter Krankheitszustände. E. R. Elste, Emmendingen, 1954, Senior Verlag, 148 pages.

The Plasma Proteins in Pregnancy. Harold C. Mack, M.D., Springfield, Ill., 1955, Charles C Thomas, 117 pages. Price $3.75. A volume of the American Lecture Series. Contains a short chapter on the fetal plasma proteins.

The Hypophyseal Growth Hormone, Nature and Actions. Edited by R. W. Smith, Jr., M.D., Oliver H. Gaebler, M.D., and C. N. H. Long, M.D., New York, 1955, McGraw-Hill Book Co., Inc., 576 pages. Price $12.00. The papers and discussion of an International Symposium held at Detroit in October, 1954, and sponsored by the Edsel S. Ford Institute for Medical Research. Twenty-nine papers were presented which discussed the present-day knowledge of the hypophyseal growth hormone from every aspect.

Reproductive System. Frank H. Netter, M.D., Summit, N. J., Ciba Pharmaceutical Products, Inc., 286 pages. Price $13.00. An atlas of Dr. Netter's illustrations of the anatomy and pathology of the reproductive system. It contains 225 color plates.

Truants From Life. Bruno Bettelheim, Glencoe, Ill., 1955, The Free Press, 511 pages. Price $6.00. The detailed discussion of four emotionally disturbed children treated at the Orthogenic School of the University of Chicago.

Amphetamine in Clinical Medicine. W. R. Bett, L. H. Howells, and A. D. Macdonald, Edinburgh and London, 1955, E. & S. Livingstone, Ltd., 78 pages. Price $2.75 (Williams & Wilkins Co., Baltimore, in U. S. A.). A small monograph intended to serve as a guide to the practitioner as when and where not to use the amphetamines clinically.

Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems, New York, 1955, Annals of the New York Academy of Sciences, 280 pages. Proceedings with papers of a conference held April 15, 1955. Seven of the papers consider the use of reserpine in infants and children.

Proceedings of the Third Medical Conference of Muscular Dystrophy, October, 1954, 324 pages. A collection of approximately fifty papers presented at the conference and which originally appeared in the *American Journal of Physical Medicine.*

Editor's Column

HYALINE MEMBRANE DISEASE

FEW subjects have been more baffling than the picture or syndrome occurring in small premature infants known as "hyaline membrane disease." Probably the term "disease" is a misnomer. In recent years many articles have been published on the subject but as yet there is no clear-cut knowledge as to just what the "membrane" represents, or as to the cause. The early view that it was due to the aspiration of amniotic fluid has been largely discredited. We have been interested in three articles recently submitted to the JOURNAL for publication and published in the last three months, as they reflect not only the wide interest in the clinical and pathological picture, but the methods of approach which are being made to explain the condition.

In the July issue Stevenson and Laufe, pediatricians, reported experimental studies in which fluids were introduced directly into the trachea of guinea pigs. This is in line with the "aspiration" theory. Ten of eighty-seven receiving a mixture of amniotic fluid and plasma developed findings in the lungs similar to those seen in the human form. In a control series where each fluid was injected separately only a plasma injection in one instance produced scattered areas of hyaline membranes. They suggest, from their findings, that the cause may be the result of aspirated amniotic fluid mixing with a pulmonary exudate.

In the August issue an interesting discussion of the dynamics of the cardiac and pulmonary circulation was presented by Lendrum, a cardiologist, who suggests that the "hyaline membrane" is a manifestation of left heart failure in the newborn premature infant. While his discussion is largely theoretical based on dynamics, the Editorial Board found his ideas of interest in a condition whose pathogenesis is unknown. A cardiac relationship has been suggested before, but, in general, has attracted little attention. It is not an idea easily approached from the experimental side.

In this issue we publish a study by Lynch and Mellor, pathologists, in regard to the nature of the membrane. Exactly what the "hyaline membrane" consists of is a moot question. It is generally referred to as a membrane, but many consider is as an exudate. Lynch and Mellor, using special chemical staining techniques, reach the conclusion that the hyaline membrane represents a highly concentrated secretion from the epithelial cells of the terminal bronchioles and alveolar ducts. Their manuscript was studied by several pathologists who were of the opinion that the findings were an important contribution.

None of the papers presents or implies a final conclusion as to the cause and nature of the condition, but they show the wide interest in the picture which some day will lead to definite conclusions as to the nature and pathogenesis of this interesting "disease."

RECOMMENDED DIETARY ALLOWANCES*

IN 1941 the Food and Nutrition Board of the National Research Council, a component of the National Academy of Sciences, adopted a set of recommended dietary allowances for calories and for a number of essential nutrients. This was published in bulletin form in 1943 and revised in 1945 and again in 1948. A recent revision made in 1953 has been recently published. Since the 1948 revision, dietary standards have been formulated for Canada, for Great Britain, and by the Food and Agriculture Organization of the United Nations. The standards recommended by the Board are for the maintenance of good nutrition in healthy persons in the United States. They differ from, and are not comparable with, the Canadian standards, as these are concerned with minimum requirements. They are closer to those formulated by the Committee on Nutrition of the British Medical Association, which are allowances intended to maintain good nutrition in the average person. The aim or purpose of the United States standards is "for the maintenance of good nutrition in substantially all normal persons," and thus are somewhat greater or broader quantitatively and include a margin of safety.

The chief change that has been made in the recommended dietary allowances is from requirements based on activity, to requirements on an age basis as used by the FAO for adult standards. The basis or starting point from which adjustments for age and activity are made is the allowance for a "standard" man and woman, aged 25, living in a temperate climate, and weighing 65 and 55 kilograms, respectively. From this basis, allowances are reduced or increased according to variations in the body build of the individual from the standard man or woman, for age differences, for work activity, and for special situations. Thus an extra allowance of 400 calories in the diet of a woman in the third trimester of pregnancy, and of 1,000 calories for the lactating woman.

Our chief interest is in the allowances for children and adolescents. These are summarized in the accompanying table taken from the report.

A few changes have been made for the pediatric age groups from the previously recommended allowance.

Calories.—Formerly recommended allowances for infants were based on an average infant 6 to 8 months of age. In the present revision the new standards, as shown in the table, are based on three age groupings, 1 to 3 months, 4 to 9 months, and 10 to 12 months, in order to take into account size, activity, and rate of growth. These are arbitrary groupings and as the report states "should be interpreted judiciously." Previous to this revision no distinction was made between the sexes in the calorie recommendation until the age of 13. To meet the increased need for energy for boys due to their greater activity, the calorie allowance for boys 10 to 12 years of age has been placed at 2,500, and for girls of the same age, 2,300. The most difficult period for standardization is the adolescent period. This is due to the

*Recommended Dietary Allowances, Revised 1953. A Report of the Food and Nutrition Board, Washington, 1954, National Academy of Sciences, National Research Council. Publication 302.

FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL
RECOMMENDED DAILY DIETARY ALLOWANCES, REVISED 1953

DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE UNITED STATES

(Allowances are considered to apply to persons normally vigorous and living in temperate climate)

	AGE YR.	WEIGHT KG.	(LB.)	HEIGHT CM.	(IN.)	CALORIES	PROTEIN GM.	CALCIUM GM.	IRON MG.	VITAMIN A I. U.	THIAMINE MG.	RIBOFLAVIN MG.	NIACIN MG.	ASCORBIC ACID MG.	VITAMIN D I. U.
Infants	0-1/12[2]														
	1/12-3/12	6	(13)	60	(24)	kg. × 120	kg. × 3.5[1]	0.6	6	1,500	0.3	0.4	3	30	400
	4/12-9/12	9	(20)	70	(28)	kg. × 110	kg. × 3.5[1]	0.8	6	1,500	0.4	0.7	4	30	400
	10/12-1	10	(22)	75	(30)	kg. × 100	kg. × 3.5[1]	1.0	6	1,500	0.5	0.9	5	30	400
Children	1-3	12	(27)	87	(34)	1,200	40	1.0	7	2,000	0.6	1.0	6	35	400
	4-6	18	(40)	109	(43)	1,600	50	1.0	8	2,500	0.8	1.2	8	50	400
	7-9	27	(59)	129	(51)	2,000	60	1.0	10	3,500	1.0	1.5	10	60	400
Boys	10-12	35	(78)	144	(57)	2,500	70	1.2	12	4,500	1.3	1.8	13	75	400
	13-15	49	(108)	163	(64)	3,200	85	1.4	15	5,000	1.6	2.1	16	90	400
	16-20	63	(139)	175	(69)	3,800	100	1.4	15	5,000	1.9	2.5	19	100	400
Girls	10-12	36	(79)	144	(57)	2,300	70	1.2	12	4,500	1.2	1.8	12	75	400
	13-15	49	(108)	160	(63)	2,500	80	1.3	15	5,000	1.3	2.0	13	80	400
	16-20	54	(120)	162	(64)	2,400	75	1.3	15	5,000	1.2	1.9	12	80	400

[1]The recommendations for infants pertain to nutrients derived primarily from cow's milk. If the milk from which the protein is derived is human milk or has been treated to render it more digestible, the allowance may be in the range of 2 to 3 grams per kilogram. There should be no question that human milk is a desirable source of nutrients for infants even though it may not provide the levels recommended for certain nutrients.

[2]During the first month of life, desirable allowances for many nutrients are dependent upon maturation of excretory and endocrine functions. Therefore no specific recommendations are given.

marked variations that occur in size at a given age resulting from differences in the rate of development. The Board considers the recommendation of the FAO at this period to be "rational," even if difficult of application to individuals. This calls for an adjustment in the age period 15 to 19 years, to the expected body size to be reached at maturity. It is recommended that the requirements be assessed at approximately 120 per cent of the standard requirement at 25. At the most, such a standard can only be a very rough guide when applied to the group or individual in the adolescent period.

Protein.—No change has been made in the protein allowance of 3.5 grams per kilogram of body weight for infants artificially fed. This is higher than the protein intake of breast-fed infants, but the Board could find no convincing evidence that the allowance for the artificially fed infants should therefore be decreased. From infancy on, the need decreases gradually from 2.5 to 3 grams in early childhood, to 1.5 to 2 grams in late childhood and adolescence, until the recommended 1 gram per kilogram for adults is reached.

Calcium.—Only one change has been made from the previously recommended allowances, an increase in the amount for girls 16 to 20 years of age, which has been placed at 1.3 grams per day. The allowance for boys at this age remains at 1.4 grams.

The previously quantitative allowances for other essential nutrients, such as iron, ascorbic acid, and vitamin D, have not been changed.

While it is exceedingly difficult to apply these standards to a specific individual, as they must be related to the total intake of the foods in the diet, they are of great value to the dietitian charged with the responsibility and task of group feeding, as children in institutions, and for agricultural planning on a national basis.

The recommended standards for the United States are not minimum standards, nor is knowledge available which would permit them to be called optimal allowances. All that the Food and Nutrition Board has attempted to do is to recommend dietary allowances which will maintain good nutrition of healthy individuals. In this revision certain changes have been made in the light of the scientific studies published between 1948 and 1953.